



ALLOSTERIC ADENOSINE RECEPTOR MODULATORS

BACKGROUND OF THE INVENTION

The present invention relates to certain thiophene derivatives and their use in the practice of medicine as allosteric modulators of adenosine receptors.

Adenosine (Ado) is an autocoid (or local hormone) that modulates numerous functions in the cardiovascular and other organ systems. The actions of Ado are mediated by at least four subtypes of cell surface receptors called A₁, A_{2a}, A_{2b}, and A₃. Because the ubiquity of adenosine receptors (AdoRs) throughout the body of a human, their indiscriminate activation may cause undesirable side effects. Therefore, new drug design approaches to achieve receptor and organ selectivity are needed.

The overall function of Ado appears to be the regulation of the balance between oxygen (or energy) supply and consumption (or work). Ado increases oxygen supply by causing vasodilation and decreases oxygen consumption or work by inhibiting cellular functions, e.g., slowing of heart rate. Consistent with this protective function, A₁AdoR agonists, Ado uptake blockers and Ado deaminase inhibitors have been shown to reduce cellular damage and dysfunction during hypoxia and ischemia. This protective role of Ado and A₁AdoR agonists has been shown in heart, brain, liver, and intestines. This and other potentially beneficial actions of Ado have led to increased interest in the development of Ado-related drugs targeted to ameliorate conditions such as myocardial ischemia and stroke.

However, the widespread expression of Ado receptors and the lack of sufficiently selective adenosine agonists have been a major impediment to the successful development of direct-acting AdoR agonists to exploit the cytoprotective properties of Ado. Therefore, other pharmacological approaches such as allosteric modulators of Ado may prove to be a valuable alternative to direct-acting Ado agonists and nucleoside uptake blockers. Such agents should selectively modulate the response to Ado in only those organs or localized areas of a given organ in which production of Ado is increased. Thus, allosteric modulators of Ado function should provide a more selective therapeutic effect than direct-acting AdoR agonists. Their action will be limited to times and locations at which significant release of Ado occurs so that systemic side effects would largely be avoided.

Allosteric modulation of the actions of Ado on the A₁AdoR by several 2-amino-3-benzoylthiophenes on cultured cells, cardiac and brain preparations have been

reported. The specificity of these compounds for A₁AdoRs have also been demonstrated.

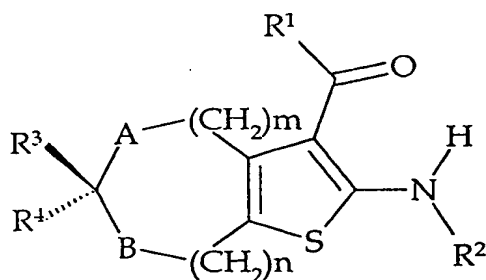
A number of compounds known to modulate the action of neurotransmitters, hormones and peptides bind at sites distinct from, but functionally linked to, the primary recognition site of the respective receptors. This form of interaction between two different ligands at the same receptor protein, which may result in modulation in the form of enhancement or inhibition of each others binding and function, is referred to as allosterism. Positive (enhancement) or negative (inhibition) allosterism is an important mechanism of action of drugs. For example, allosteric interactions between the GABA receptor and benzodiazepines, to atrial natriuretic factor (ANF) receptor and amiloride, the dextromethorphan binding site and ropizine, and the muscarinic receptor and gallamine have been described. The compounds of the present invention have been found to be potent, yet selective allosteric modulators of AdoR agonists, and in some cases, AdoR antagonists.

BRIEF SUMMARY OF THE INVENTION

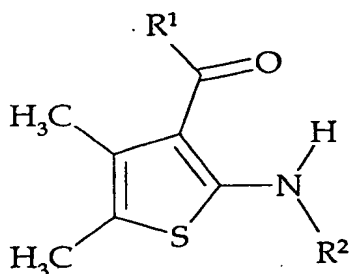
Compounds useful as potent, yet selective allosteric modulators of adenosine receptors, with activity as AdoR agonists, and, in come cases AdoR antagonists, and methods of preparation and use thereof, are disclosed.

The compounds have the following general formulas IA and 1B:

(IA)



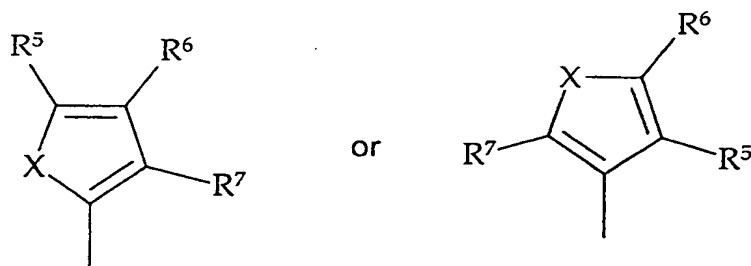
or



(IB)

wherein:

R¹ is



wherein R² is H, C(=O)R⁸;

R⁸ is H, alkyl, substituted alkyl, aralkyl, substituted aralkyl, aryl, or substituted aryl;

5 R³ and R⁴ are independently H, alkyl, substituted alkyl, aryl, substituted aryl, aralkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, hydroxy, alkylsulfonyloxy, arylsulfonyloxy, substituted arylsulfonyloxy, alkoxy, alkylthio, or arylthio;

or if R³ and R⁴ are both alkoxy or alkylthio, may form a 1,3-dioxolan-2-yl, 1,3-

10 dioxan-2-yl, 1,3-dithiolan-2-yl, or 1,3-dithian-2-yl group;

or together R³ and R⁴ may form a carbonyl oxygen;

R⁵, R⁶, and R⁷ are independently H, alkyl, substituted alkyl, aryl, substituted aryl, halogen, hydroxy, nitro, amino, substituted amino, disubstituted amino, alkoxy, aryloxy, alkylthio, arylthio, sulfonamido, or substituted sulfonamido;

15 or together R⁵ and R⁶ or R⁶ and R⁷ may be CH=CH-CH=CH, such that they form a fused aromatic ring;

A and B are independently O, S, or N-R⁸;

or A and B may independently represent a carbon-carbon single bond;

m and n are independently 0, 1, 2, or 3;

20 except that A and B cannot both represent a carbon-carbon single bond when m and n are both 0;

and X is CH=CH, CH=N, N=CH, O, S, or N-R⁸.

The compounds can be used in a method for cardioprotection, neuroprotection, pain management, reduction of free fatty acids, triglycerides, or glucose levels,

25 adjunct therapy in diabetes, treatment of GI disorders, treatment of glaucoma; treatment of sleep disorders; treatment of cardiac disarrhythmias (peroxysmal supraventricular tachycardia, treatment of congestive heart failure or treatment of inflammation.

The compounds can be used in a pharmaceutical formulation that includes a compounds of formulas IA or IB and one or more excipients. Various chemical intermediates can be used to prepare the compounds of formula IA or 1B:

5 **BRIEF DESCRIPTION OF THE DRAWINGS**

Not applicable.

DETAILED DESCRIPTION OF THE INVENTION

10 The present application discloses compounds useful as potent, yet selective allosteric modulators of adenosine receptors, with activity as AdoR agonists, and in some cases, AdoR antagonists, and methods of preparation and use thereof.

The compounds can be used in a method for allosterically modulating adenosine receptors in a mammal, including a human. The methods involve administering an effective amount of a compound of formula IA or 1B sufficient to moderate
15 adenosine receptors to the mammal.

The compounds can be used in a pharmaceutical formulation that includes a compound of formula IA or IB and one or more excipients. Various chemical intermediates can be used to prepare the compounds of formula IA or IB.

As used herein the term "lower alkyl" means a monovalent radical, straight or
20 branched chain, derived from the corresponding alkane having one to ten carbon atoms, i.e., methyl, ethyl, propyl, Isopropyl, n-butyl, sec-butyl, t-butyl, pentyl (all isomers), etc. Likewise, "lower alkylene" means a divalent radical of the corresponding alkane. Further, as used herein, other moieties having names derived from alkanes, such as alkoxyl, alkanoyl, alkenyl, cycloalkenyl, etc when
25 modified by "lower," have carbon chains of ten or less carbon atoms. In those cases where the minimum number of carbons are greater than one, e.g., alkenyl (minimum of two carbons) and cycloalkyl, (minimum of three carbons), it is to be understood that "lower" means at least the minimum number of carbons.

As used herein the term "amino acid" means an alpha amino acid selected from
30 those amino acids which naturally occur in proteins but without regard for specific stereochemical properties. The term "protected amino acid" means an amino acid of which the alpha amino group has been converted to a less reactive moiety, but a moiety which can be converted back to the amino group with relative ease. The terms "amino acid residue" and "amino acid moiety" are use synonymously herein.

35 As used herein, the term "substituted alkyl" refers to an alkyl group, preferably of from 1 to 10 carbon atoms, ("substituted lower alkyl"), having from 1 to 5

substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyacylamino, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO, heteroaryl, -S(=O)-alkyl, -S(=O)-substituted alkyl, -S(=O)-aryl, -S(=O)-heteroaryl, and mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, aryl, heteroaryl and heterocyclic. As used herein, other moieties having, the prefix "substituted" are intended to include one or more of the substituents listed above. As used herein, the term "alkoxy" refers to the group "alkyl-O-", where alkyl is as defined above. Preferred alkoxy groups include, by way of example, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, and the like.

As used herein, the term "alkenyl" refers to alkenyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation. Preferred alkenyl groups include ethenyl (-CH=CH₂), n-propenyl (-CH₂CH=CH₂), iso-propenyl (-C(CH₃)=CH₂), and the like.

As used herein, the term "alkynyl" refers to alkynyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkynyl unsaturation.

As used herein, the term "acyl" refers to the groups alkyl-C(O)-, substituted alkyl C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)- and heterocyclic-C(O)-where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic are as defined herein.

As used herein, the term "acylamino" refers to the group -C(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, or heterocyclic, wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

As used herein, the term "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring, (e.g., phenyl) or multiple

condensed (fused) rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like. Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with from 1 to 5 substituents and preferably 1 to 3 substituents selected from the group consisting of acyloxy, hydroxy, acyl, alkyl, alkoxy, alkenyl, alkynyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -S02-alkyl, -S02-substituted alkyl, -S02-aryl, -S02-heteroaryl; trihalomethyl. Preferred substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

As used herein, the term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 12 carbon atoms having a single cyclic ring or multiple condensed rings: Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

As used herein, the terms "halo" or "halogen" refer to fluoro, chloro, bromo and iodo and preferably is either fluoro or chloro.

As used herein, the term "heteroaryl" refers to an aromatic carbocyclic group of from 1 to 15 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within at least one ring (if there is more than one ring).

Unless otherwise constrained by the definition for the heteroaryl substituent, such heteroaryl groups can be optionally substituted with from 1 to 5 substituents and preferably 1 to 3 substituents selected from the group consisting of acyloxy, hydroxy, acyl, alkyl, alkoxy, alkenyl, alkynyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -S02-alkyl, -S02-substituted alkyl, -S02-aryl, -S02-heteroaryl, trihalomethyl. Preferred substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy. Such

heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl).

“Heterocycle” or “heterocyclic” refers to a monovalent saturated or unsaturated carbocyclic group having a single ring or multiple condensed rings, from 1 to 15 carbon atoms and from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur or oxygen within the ring. Such heterocyclic groups are optionally substituted with 1 to 5 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, aryloxy, halo, nitro, heteroaryl, thiol, thioalkoxy, substituted thioalkoxy, thioaryloxy, trihalomethyl, and the like.

Such heterocyclic groups can have a single ring or multiple condensed rings.

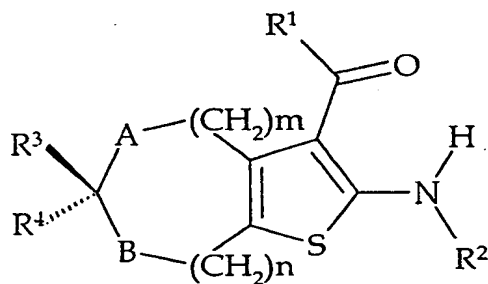
As to any of the above groups that contain 1 or more substituents, it is understood, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible.

“Pharmaceutically acceptable salts” refers to pharmaceutically acceptable salts of a compound of Formulas IA or IB, which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like can be used as the pharmaceutically acceptable salt.

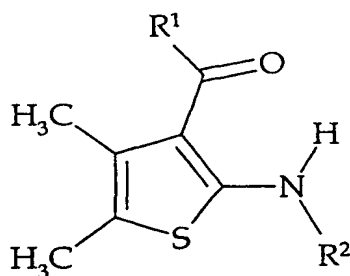
The term “protecting group” or “blocking group” refers to any group which when bound to one or more hydroxyl, amino or carboxyl groups of the compounds (including intermediates thereof such as the aminolactams, aminolactones, etc.)

prevents reactions from occurring at these groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the hydroxyl, amino or carboxyl group. Preferred removable amino blocking groups include conventional substituents such as t-butyloxycarbonyl (t-BOC), benzyloxycarbonyl (CBZ), and the like which can be removed by conventional conditions compatible with the nature of the product.

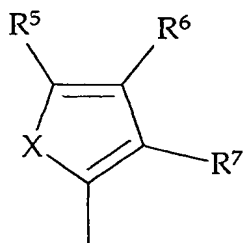
The compounds of the present invention have the following general formulas IA and IB:
(IA)



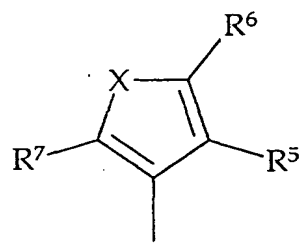
or
(IB)



5 wherein:
R¹ is



or



wherein R² is H, C(=O)R⁸;

R⁸ is H, alkyl, substituted alkyl, aralkyl, substituted aralkyl, aryl, or substituted
10 aryl;

R³ and R⁴ are independently H, alkyl, substituted alkyl, aryl, substituted aryl,
aralkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen,
hydroxy, alkylsulfonyloxy, arylsulfonyloxy, substituted arylsulfonyloxy, alkoxy,
alkylthio, or arylthio;

15 or if R³ and R⁴ are both alkoxy or alkylthio, may form a 1,3-dioxolan-2-yl, 1,3-
dioxan-2-yl, 1,3-dithiolan-2-yl, or 1,3-dithian-2-yl group;
or together R³ and R⁴ may form a carbonyl oxygen;

R⁵, R⁶, and R⁷ are independently H, alkyl, substituted alkyl, aryl, substituted aryl, halogen, hydroxy, nitro, amino, substituted amino, disubstituted amino, alkoxy, aryloxy, alkylthio, arylthio, sulfonamido, or substituted sulfonamido;

or together R⁵ and R⁶ or R⁶ and R⁷ may be CH=CH-CH=CH, such that they form a fused aromatic ring;

A and B are independently O, S, or N-R⁸;

or A and B may independently represent a carbon-carbon single bond;

m and n are independently 0, 1, 2, or 3;

except that A and B cannot both represent a carbon-carbon single bond

when m and n are both 0; and

X is CH=CH, CH=N, N=CH, O, S, or N-R⁸.

Those skilled in the art of organic chemistry will appreciate that reactive and fragile functional groups often must be protected prior to a particular reaction, or sequence of reactions, and then restored to their original forms after the last

reaction is completed. Usually groups are protected by converting them to a relatively stable derivative. For example, a hydroxyl group may be converted to an ether group and an amino converted to an amide or carbamate. Methods of protecting and de-protect, also know as "blocking" and "de-blocking," are well know and widely practiced in the art, e.g., see T. Green, *Protective Groups in Organic Synthesis*, John Wiley, New York (1981) or *Protective Groups in Organic Chemistry*, Ed. J.F.W. McOmie, Plenum Press, London (1973).

Representative example compounds of the present invention include:

| Example Compound Number | Compound Name |
|-------------------------|---|
| 1 | (2-Amino-4,7-dihydro-5H-thieno[2,3-c]thiopyran-3-yl)-phenyl-methanone |
| 2 | (2-Amino-4,7-dihydro-5H-thieno[2,3-c]thiopyran-3-yl)-(4-chlorophenyl)-methanone |
| 3 | (2-Amino-4,5-dihydrothieno[2,3-b]thiophen-3-yl)-(4-chlorophenyl)-methanone |
| 4 | (2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-furan-2-yl-methanone |

| Example Compound Number | Compound Name |
|-------------------------|--|
| 5 | 2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-thiophen-2-yl-methanone |
| 6 | (2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-naphthalen-1-yl-methanone |
| 7 | (2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-naphthalen-1-yl-methanone |
| 8 | (2-Amino-4,5-dimethylthiophen-3-yl)-naphthalen-1-yl-methanone |
| 9 | (2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-naphthalen-1-yl-methanone |
| 10 | N-[3-(Furan-2-carbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl]-acetamide |
| 11 | (2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-furan-2-yl-methanone |
| 12 | (2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-furan-2-yl-methanone |
| 13 | (2-Amino-4,5-dimethylthiophen-3-yl)-furan-2-yl-methanone |
| 14 | (2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-benzofuran-2-yl-methanone |
| 15 | (2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-benzofuran-2-yl-methanone |
| 16 | (2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-benzofuran-2-yl-methanone |
| 17 | 2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-pyridin-2-yl-methanone |
| 18 | (2-Amino-4,5-dimethylthiophen-3-yl)-benzofuran-2-yl-methanone |
| 19 | (2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-pyridin-2-yl-methanone |
| 20 | (2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-pyridin-2-yl-methanone |
| 21 | (2-Amino-4,5-dimethylthiophen-3-yl)-pyridin-2-yl-methanone |

| Example Compound Number | Compound Name |
|-------------------------------|---|
| 22 | (2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-(4-bromonaphthalen-1-yl)-methanone |
| 23 | (2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-(4-methoxynaphthalen-1-yl)-methanone |
| 24 | (2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-(4-iodonaphthalen-1-yl)-methanone |
| 25 | (2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-(4-chloronaphthalen-1-yl)-methanone |
| 26 | (2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-iodonaphthalen-1-yl)-methanone |
| 27 | (2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-methoxynaphthalen-1-yl)-methanone |
| 28 | (2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-chloronaphthalen-1-yl)-methanone |
| 29 | (2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-bromonaphthalen-1-yl)-methanone |
| 30 | (2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-naphthalen-2-yl-methanone |
| 31 | (2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-naphthalen-2-yl-methanone |
| 32 | (2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-naphthalen-2-yl-methanone |
| 33 | (2-Amino-4,5-dimethylthiophen-3-yl)-naphthalen-2-yl-methanone |
| 34 | (2-Amino-6-spiro(1,4-dioxolan-2-yl)-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-chlorophenyl)-methanone |
| 35 | (2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-thiophen-2-yl-methanone |
| 36 | (2-Amino-4,5-dimethylthiophen-3-yl)-thiophen-2-yl-methanone |
| 37 | (2-Amino-6-hydroxy-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-chloro-phenyl)-methanone |

| Example Compound Number | Compound Name |
|-------------------------------|---|
| 38 | (2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-thiophen-2-yl-methanone |
| 39 | (2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(5-bromothiophen-2-yl)-methanone |
| 40 | (2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-(5-bromothiophen-2-yl)-methanone |
| 41 | (2-Amino-4,5-dimethylthiophen-3-yl)-(5-bromothiophen-2-yl)-methanone |
| 42 | (2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-(5-bromothiophen-2-yl)-methanone |
| 43 | (2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(5-chlorothiophen-2-yl)-methanone |
| 44 | (2-Amino-5,6-dihydrocyclopenta[b]thiophen-3-yl)-(5-chlorothiophen-2-yl)-methanone |
| 45 | (2-Amino-4,5-dimethylthiophen-3-yl)-(5-chlorothiophen-2-yl)-methanone |
| 46 | (2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-(5-chloro-thiophen-2-yl)-methanone |
| 47 | (2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-thiophen-3-yl-methanone |
| 48 | (2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-thiophen-3-yl-methanone |
| 49 | (2-Amino-4,5-dimethylthiophen-3-yl)-thiophen-3-yl-methanone |
| 50 | (2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-thiophen-3-yl-methanone |
| 51 | [2-Amino-6-(4-methoxyphenyl)-4H-1,5,7-trithia-inden-3-yl]-naphthalen-1-yl-methanone |
| 52 | [2-Amino-6-(4-methoxyphenyl)-4H-1,5,7-trithia-inden-3-yl]-(4-chlorophenyl)-methanone |

| Example Compound Number | Compound Name |
|-------------------------|---|
| 53 | [2-Amino-6-(4-methoxyphenyl)-4H-1,5,7-trithia-inden-3-yl]-thiophen-2-yl-methanone |
| 54 | 2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(9H-fluoren-2-yl)-methanone |
| 55 | (2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-(9H-fluoren-2-yl)-methanone |
| 56 | 2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-(9H-fluor-en-2-yl)-methanone |
| 57 | [2-Amino-6-[(methanesulfonyl)oxy]-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl]-(4-chlorophenyl)-methanone |
| 58 | [2-Amino-6-(4-chlorobenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl]-naphthalen-2-yl-methanone |
| 59 | 2-Amino-6-(4-fluorobenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl]-naphthalen-2-yl-methanone |
| 60 | (2-Amino-6-benzyl-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-naphthalen-2-yl-methanone |
| 61 | [2-Amino-6-(2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl]-naphthalen-2-yl-methanone |
| 62 | [2-Amino-6-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl]-naphthalen-2-yl-methanone |
| 63 | [2-Amino-6-(3,4,5-trimethoxybenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyri-din-3-yl]-naphthalen-2-yl-methanone |
| 64 | (2-Amino-6-benzyl-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-thiophen-2-yl-methanone |
| 65 | (2-Amino-6-benzyl-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-thiophen-3-yl-methanone |
| 66 | (2-Amino-6-benzyl-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-chlorophenyl)-methanone |
| 67 | (2-Amino-6-benzyl-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-naphthalen-2-yl-methanone |

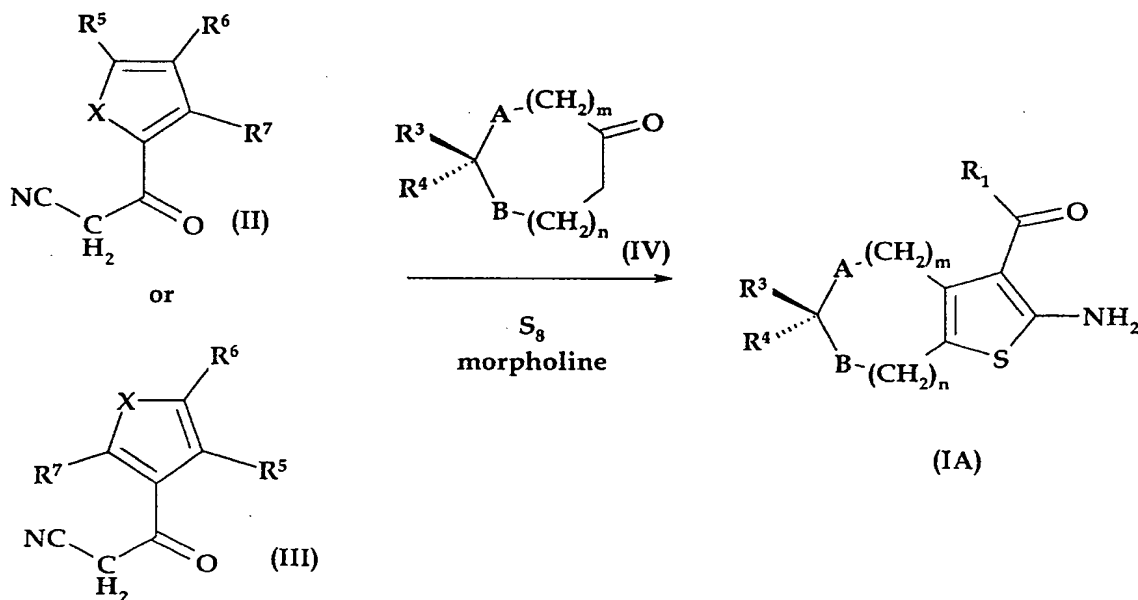
| Example Compound Number | Compound Name |
|-------------------------|---|
| 68 | [2-Amino-6-(4-nitrobenzyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl]-naphthalen-2-yl-methanone |

SYNTHESIS OF COMPOUNDS

Compounds of formula 1A may be conveniently prepared according to

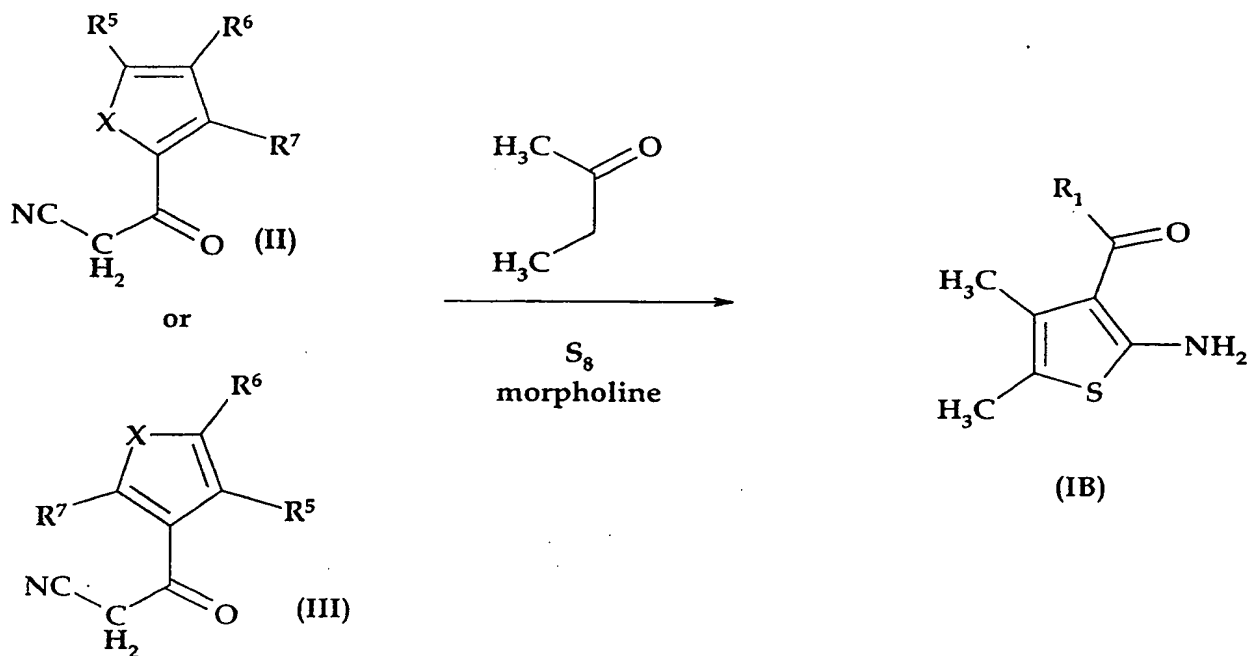
- Scheme 1.** A compound of formula (II) or (III) is reacted with a compound of formula (IV) in the presence of elemental sulfur and morpholine at approximately 70 °C, for about one hour, then at approximately 20 to 25 °C for a period of about 20 hours to yield a compound of formula (IA).

SCHEME 1



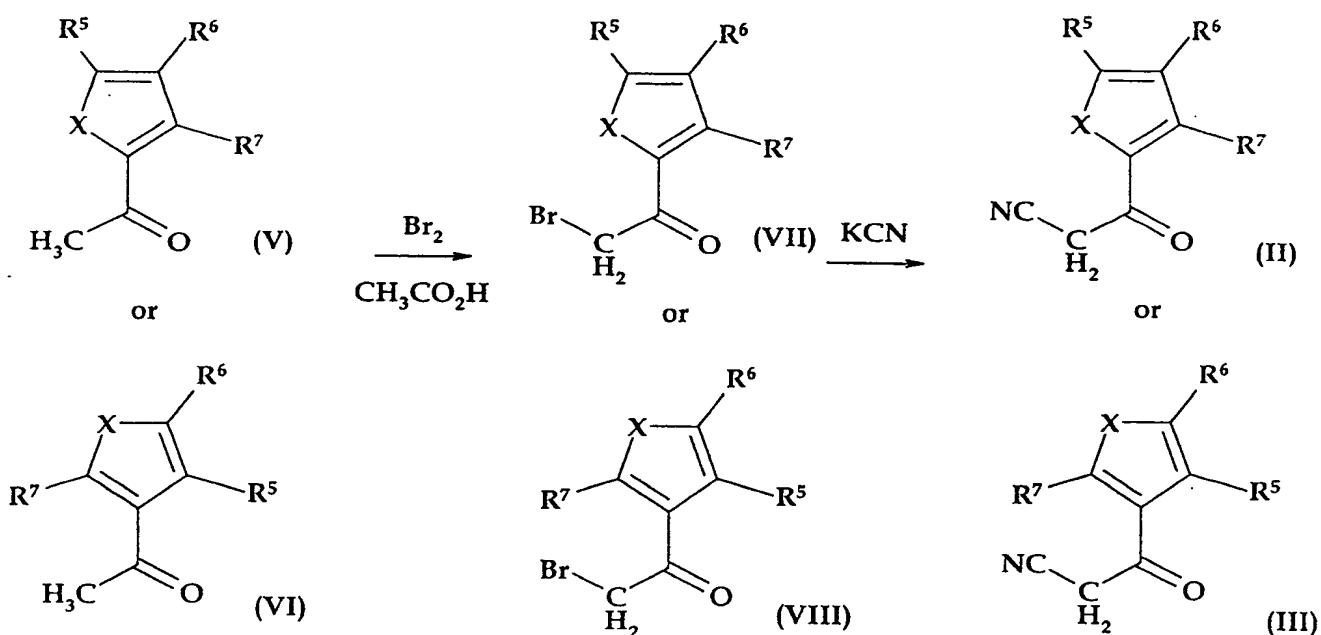
- Compounds of formula (IB) may be conveniently prepared according to **Scheme 2**. In a manner analogous to that used for preparing compounds of formula (IA), 2-butanone is reacted with a compound of formula (II) or (III) in the presence of elemental sulfur and morpholine at approximately 70 °C, for about one hour, then at approximately 20 to 25 °C, for a period of about 20 hours, to afford a compound of formula (IB).

SCHEME 2



Compounds of formula (II) or (III) may be conveniently prepared according to Scheme 3 by treating compounds of formula (V) or (VI) with bromine in glacial acetic acid at approximately 20 to 25 °C for approximately two hours to provide intermediates of formula (VII) or (VIII). These intermediates in a protic solvent, such as ethanol, may then be treated with an aqueous solution of potassium cyanide at approximately 20 to 25 °C for about 20 to 24 hours to afford compounds of formula (II) or (III).

SCHEME 3



Compounds of formula (IV), (V), or (VI) are commercially available or may be prepared by methods known in the literature.

UTILITY

The compounds can be used for:

Protection against hypoxia and/or ischemia induced injuries (e.g., stroke, infarction);

Treatment of adenosine-sensitive cardiac arrhythmias;

antinociception (i.e., analgesics);

anticonvulsants;

cardioprotection, short term (e.g., prior to percutaneous angioplasty (PTDA),

angioplasty, and cardiac surgeries) and long term (prevention of myocardial

infarction, especially in high risk patients, reduction of infarct damage, especially in high risk patients);

treatment of congestive heart failure;

neuroprotection: stroke prevention, stroke treatment, treatment of Alzheimer's

disease and treatment of epilepsy;

pain management generally, including different forms of neuropathic pain, e.g.,

diabetic neuropathy, post herpetic neuralgia;

antilipid uses: reduction of free fatty acids, triglycerides, glucose;
adjunct therapy in diabetes, including, insulin dependent and non-insulin
dependent diabetes mellitus: stimulation of insulin secretion from the pancreas,
increase in tissue sensitivity to insulin;

- 5 treatment of GI disorders such as diarrhea, irritable bowel disease, irritable bowel
syndrome, irritable bladder, incontinence such as urge incontinence;
treatment of glaucoma;
treatment of sleep disorders, such as sleep apnea;
treatment of cardiac dysarrhythmias (paroxysmal supraventricular tachycardia;
10 use in combination with anesthesia for post surgical pain;
treatment of inflammation;
diagnostic uses, for example, to determine the presence of one or more of the above
described medical conditions, or in a screening assay to determine the effectiveness
of other compounds for binding to the A₁ Ado receptor (i.e., through competitive
15 inhibition as determined by various binding assays); and
Other indications for which A₁AdoR agonists are used.

The amount of compound of the present invention required to be effective as an
allosteric modulator of an adenosine receptor will, of course, vary with the
individual mammal being treated and is ultimately at the discretion of the medical
20 or veterinary practitioner. The factors to be considered include the condition being
treated, the route of administration, the nature of the formulation, the mammal's
body weight, surface area, age and general condition, and the particular compound
to be administered. However, a suitable effective dose is in the range of about 0.1
µg/kg to about 10 mg/kg body weight per day, preferably in the range of about 1
25 mg/kg to about 3 mg/kg per day.

The total daily dose may be given as a single dose, multiple doses, e.g., two to six
times per day, or by intravenous infusion for a selected duration. Dosages above or
below the range cited above are within the scope of the present invention and may
be administered to the individual patient if desired and necessary. For example, for
30 a 75 kg mammal, a dose range would be about 75 mg to about 220 mg per day,
and a typical dose would be about 150 mg per day. If discrete multiple doses are
indicated, treatment might typically be 50mg of a compound of the present
invention given 3 times per day.

BIOLOGICAL ASSAYS.

Chinese hamster ovary cells expressing human recombinant A₁ adenosine receptors (CHO:huA₁ cells) at a density of approximately 8000 fmol/mg protein were prepared as previously described (Kollias-Baker et al., (1997), *J. Pharmacol. Exp.*

5 *Ther.* **281**: 761-768) and aliquots of the cells at low passage numbers were frozen and stored in liquid nitrogen. When compounds were tested, an aliquot of CHO:huA₁ cells were rapidly thawed after removal from liquid nitrogen, then grown in Ham's F12 culture medium with 10% fetal bovine serum and 0.5 mg/mL of antibiotic G-418 (Shryock, Ozeck, and Belardinelli (1998), *Mol. Pharmacol* **53**: 886-
10 893). Cells were passaged thrice weekly. Aliquots of cells were placed into 12-well plates with culture medium, serum, and antibiotic for 48 hours, by which time the cells had grown to a confluent monolayer.

Allosteric enhancement was measured as the action of a test compound at different concentrations (0.01, 0.1, 1 and 10 μ M) to reduce the cAMP content of CHO:huA₁
15 cells. To initiate an experiment, growth medium was removed from the 12-well plates and cells were washed once with warm Hanks' buffered saline. The wash solution was then removed and replaced with fresh Hanks' solution containing forskolin (1 μ M), rolipram (20 μ M), N⁶-cyclopentyladenosine (CPA, 0.01 nM), adenosine deaminase (2 U/mL), and the test compound. Forskolin was used to
20 stimulate the activity of adenylyl cyclase, rolipram to inhibit cAMP phosphodiesterase, adenosine deaminase to degrade endogenous adenosine, and CPA to cause a small increase of the number of activated adenosine receptors. After 6 min of incubation at 36 °C in the presence of test compound, the incubation solution was removed and hydrochloric acid (final concentration 50 mM) was added
25 to terminate drug action.

The content of cAMP in acidified extracts of cells was determined by radioimmunoassay as previously described (Kollias-Baker et al., (1997), *J. Pharmacol. Exp. Ther.* **281**: 761-768). Because the magnitude of the effects of allosteric enhancers on CHO:huA₁ cells changed subtly with passage number and
30 differed slightly among different aliquots of cells, the actions of the test compounds and the action of a reference compound (PD 81,723) were assessed in each experiment. The effect of each test compound on cAMP content is presented in **Table 1** as a percentage of the value of cAMP content in the absence of drug (control, 100%). Each value is a mean \pm standard error of 6 determinations in each
35 of the number of experiments indicated in the "n" column of the table.

TABLE 1

**Perc ntage Change in CHO Cell cAMP Cont nt in Pr s nce of 2-Amino-3-Acyl-
Thioph n s**

| Example Compound Number | n | Change in cAMP Content from Control (mean + SEM) | | | |
|-------------------------------|----|--|--------|--------|--------|
| | | Concentration of Test Compound | | | |
| | | 0.01 mm | 0.1 mm | 1 mm | 10 mm |
| 1 | 3 | 9±4 | -6±3 | -15±2 | -35±2 |
| 2 | 3 | 15±3 | -10±4 | 16±5 | -0.3±5 |
| 3 | 3 | -1±4 | 11±4 | 1±3 | -35±4 |
| 4 | 3 | -10±2 | 2±6 | -3±6 | -10±7 |
| 5 | 3 | -11±3 | -11±5 | -16±3 | -40±2 |
| 6 | 3 | -11±4 | -15±4 | -22±3 | -52±3 |
| 7 | 3 | -0.6±3 | -6±1 | -29±4 | -60±1 |
| 8 | 3 | -0.6±2 | -3±3 | 6±5 | -45±2 |
| 9 | 3 | -21±3 | -7±4 | -25±4 | 19±2 |
| 10 | 3 | -8±5 | -14±4 | -25±5 | 8±5 |
| 11 | 3 | 3±4 | -14±4 | -0.8±3 | -23±2 |
| 12 | 3 | -27±4 | -0.6±4 | -15±3 | -8±11 |
| 13 | 3 | -4±5 | 11±5 | -7±5 | 5±10 |
| 14 | 3 | -13±5 | -3±4 | -4±3 | -5±4 |
| 15 | 3 | -5±3 | -13±3 | 3±5 | -4±6 |
| 16 | 3 | 4±3 | 14±4 | -10±2 | 11±4 |
| 17 | 3 | -3±4 | 0.8±7 | -1±6 | 2±7 |
| 18 | 3 | 6±5 | -7±4 | 16±5 | 7±6 |
| 19 | 3 | -2±4 | -8±5 | -11±5 | 8±3 |
| 20 | 3 | 2±4 | 7±5 | 0.1±5 | 31±3 |
| 21 | 3 | 0.7±3 | -8±3 | 4±4 | 14±4 |
| 22 | 3 | 3±3 | 19±5 | -14±5 | -67±3 |
| 23 | 3 | -6±3 | -3±4 | -8±4 | -35±3 |
| 24 | 3 | -6±3 | -8±3 | -22±4 | -75±1 |
| 25 | 3 | -10±2 | -15±4 | -27±2 | -55±2 |
| 26 | 3 | -3±4 | -4±4 | -24±5 | -67±2 |
| 27 | 3 | 5±4 | -5±4 | -3±3 | -17±1 |
| 28 | 3 | -11±3 | 3±3 | -25±4 | -44±2 |
| 29 | 3 | -6±3 | -10±2 | -29±2 | -72±1 |
| 30 | 3 | -13±4 | -24±3 | -28±2 | -42±3 |
| 31 | 3 | -19±3 | -14±4 | -15±3 | -51±3 |
| 32 | 3 | -11±4 | -12±3 | -18±3 | -60±4 |
| 33 | 3 | -1±3 | -4±3 | -8±3 | -28±3 |
| PD 81,723 | 33 | -1±2 | -7±2 | -13±1 | -50±1 |

RADIOLIGAND BINDING ASSAYS RESULTS

Methods for detecting specific macromolecular species, such as proteins, drugs, and polynucleotides, have proven to be very valuable analytical techniques in biology and medicine, particularly for characterizing the molecular composition of normal and abnormal tissue samples and genetic material. Many different types of such detection methods are widely used in biomedical research and clinical laboratory medicine. Examples of such detection methods include: immunoassays, immunochemical staining for microscopy, fluorescence-activated cell sorting (FACS), nucleic acid hybridization, water sampling, air sampling, and others.

Typically, a detection method employs at least one analytical reagent that binds to a specific target macromolecular species and produces a detectable signal. These analytical reagents typically have two components: (1) a probe macromolecule, for example, an antibody or oligonucleotide, that can bind a target macromolecule with a high degree of specificity and affinity, and (2) a detectable label, such as a radioisotope or covalently-linked fluorescent dye molecule. In general, the binding properties of the probe macromolecule define the specificity of the detection method, and the detectability of the associated label determines the sensitivity of the detection method. The sensitivity of detection is in turn related to both the type of label employed and the quality and type of equipment available to detect it.

For example, radioimmunoassays (RIA) have been among the most sensitive and specific analytical methods used for detecting and quantitating biological macromolecules. Radioimmunoassay techniques have been used to detect and measure minute quantities of specific analytes, such as polypeptides, drugs, steroid hormones, polynucleotides, metabolites, and tumor markers, in biological samples. Radioimmunoassay methods employ immunoglobulins labeled with one or more radioisotopes as the analytical reagent. Radiation (alpha, beta, or gamma) produced by decay of the attached radioisotope label serves as the signal which can be detected and quantitated by various radiometric methods.

The term "labeled analog" is further understood to encompass compounds which are labeled with radioactive isotopes, such as but not limited to tritium (^3H), carbon (^{14}C), iodine (^{125}I), phosphorus (^{31}P , ^{32}P , ^{33}P), sulfur (^{35}S) or otherwise labeled (e.g. fluorescently). Less common, but also known in the art, is the use of radio labels of the positron emitting radionuclides ^{11}C , ^{13}N , ^{15}O , ^{18}F or ^{76}Br . Also known in the art, but less common, is the use of stable isotopes, such as deuterium (^2H) and ^{13}C that are detected by magnetic resonance imaging or mass spectrometry. The compounds of this invention may be labeled or derivatized, for example, for kinetic binding

experiments, for further elucidating metabolic pathways and enzymatic mechanisms, or for characterization by methods known in the art of analytical chemistry.

5 **FORMULATIONS**

Formulations of the present invention for medical use comprise an active compound, i.e., a compound of formula (IA), (IB) or (IC), together with an acceptable carrier thereof and optionally other therapeutically active ingredients. The carrier must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The present invention, therefore, further provides a pharmaceutical formulation comprising a compound of formula (IA), (IB) or (IC) together with a pharmaceutically acceptable carrier thereof.

The formulations include, but are not limited to, those suitable for oral, rectal, topical or parenteral (including subcutaneous, intramuscular and intravenous) administration. Preferred are those suitable for oral or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active compound into association with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier or a finely divided solid carrier and then, if necessary, shaping the product into desired unit dosage form.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound; as a powder or granules; or a suspension or solution in an aqueous liquid or non-aqueous liquid, e.g., a syrup, an elixir, an emulsion or a draught.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form, e.g., a powder or granules, optionally mixed with accessory ingredients, e.g., binders, lubricants, inert diluents, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered active compound with any suitable carrier.

A syrup or suspension may be made by adding the active compound to a concentrated, aqueous solution of a sugar, e.g., sucrose, to which may also be added any accessory ingredients. Such accessory ingredients may include flavoring, an agent to retard crystallization of the sugar or an agent to increase the solubility of any other ingredient, e.g., as a polyhydric alcohol, for example, glycerol or sorbitol.

Formulations for rectal administration may be presented as a suppository with a conventional carrier, e.g., cocoa butter or Witepsol S55 (trademark of Dynamite Nobel Chemical, Germany), for a suppository base.

Formulations suitable for parenteral administration conveniently comprise sterile aqueous preparation of the active compound which is preferably isotonic with the blood of the recipient. Thus, such formulations may conveniently contain distilled water, 5% dextrose in distilled water or saline. Useful formulations also comprise concentrated solutions or solids containing the compound of formula (I) which upon dilution with an appropriate solvent give a solution suitable for parental administration above.

Topical formulations include ointments, creams, gels and lotions which may be prepared by conventional methods known in the art of pharmacy. In addition to the ointment, cream gel, or lotion base and the active ingredient, such topical formulation may also contain preservatives, perfumes, and additional active pharmaceutical agents.

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more optional accessory ingredient(s) utilized in the art of pharmaceutical formulations, e.g., diluents, buffers, flavoring agents, binders, surface active agents, thickeners, lubricants, suspending agents, preservatives (including antioxidants) and the like.

EXAMPLES

The following examples illustrate aspects of this invention but should not be construed as limitations. The symbols and conventions used in these examples are indented to be consistent with those used in the contemporary, international, chemical literature, for example, the *Journal of the American Chemical Society* and *Tetrahedron*.

EXAMPLE 1

(2-Amino-4,7-dihydro-5H-thieno[2,3-c]thiopyran-3-yl)-phenyl-methanone

Step A. 2-Bromoacetophenone: To a solution of acetophenone (10 mmol, Aldrich) in 10 ml of glacial acetic acid, was added bromine (10 mmol, 0.51 mL) dropwise and the mixture was stirred at room temperature for 2 h. After this time, the acetic acid was evaporated under reduced pressure at a temperature lower than 40 °C. The crude product so obtained was used for the next reaction without purification.

Step B. Benzoylacetonitrile: The crude 2-bromoacetophenone, previously prepared in Step A, was dissolved in 95% EtOH (15 ml). A solution of potassium cyanide (3.6 g, 55 mmol), dissolved in water (5 ml), was added in one portion and the mixture was stirred at room temperature for 24 h. The mixture was then poured onto a mixture of crushed ice and water and acidified with glacial acetic acid (pH = 5-6). The resulting solid was collected by filtration and washed with water.

Step C. (2-Amino-4,7-dihydro-5H-thieno[2,3-c]thiopyran-3-yl)-phenyl-methanone: A mixture of benzoylacetonitrile (5 mmol, prepared in Step B), tetrahydro-4H-thiopyran-4-one (5 mmol, Aldrich), morpholine (0.44 mL, 5 mmol), and sulfur (164 mg, 5 mmol) was heated at 70 °C for 1 h, then stirred at room temperature for 20 h. At the end of this period, the solvent was evaporated under reduced pressure and the residue diluted with ethyl acetate. After washing with water, the organic layer was dried over Na₂SO₄, filtered, and evaporated. The crude product was purified by flash column chromatography, then recrystallized from petroleum ether.

Yield: 68%; ¹H NMR (CDCl₃): δ 2.18 (t, 2H, J=5.6 Hz), 2.58 (t, 2H, J=5.6 Hz), 3.63 (s, 2H), 6.57 (bs, 2H), 7.51 (m, 5H); yellow solid, mp: 92-95 °C (petroleum ether).

In an analogous manner, the following compounds are prepared by the procedures of Scheme 1 taught above in Example 1, using appropriate precursor compounds, as indicated. If the appropriate precursors are not available, they are prepared as indicated in the following examples:

EXAMPLE 2

(2-Amino-4,7-dihydro-5H-thieno[2,3-c]thiopyran-3-yl)-(4-chlorophenyl)-methanone

The procedure of Example 1 was followed except that 4-chloroacetophenone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(4-chlorobenzoyl)acetonitrile (Steps A and B). Tetrahydro-4H-thiopyran-4-one (Aldrich), 2-(4-chlorobenzoyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 66%; ¹H NMR (CDCl₃): δ 2.18 (t, 2H, J=5.6 Hz), 2.60 (t, 2H, J=5.6 Hz), 3.63 (s, 2H), 6.62 (bs, 2H), 7.39 (d, J=7.6 Hz, 2H), 7.47 (d, J=7.6 Hz, 2H); yellow solid, mp: 142-146 °C (petroleum ether).

EXAMPLE 3

(2-Amino-4,5-dihydrothieno[2,3-b]thiophen-3-yl)-(4-chlorophenyl)-methanone

The procedure of Example 1 was followed except that 4-chloroacetophenone

(Aldrich) was used in place of acetophenone to prepare the corresponding 2-(4-

chlorobenzoyl)acetonitrile (Steps A and B). Tetrahydrothiophen-3-one (Aldrich), 2-

(4-chlorobenzoyl)acetonitrile, morpholine, and sulfur were reacted according to the

procedure of Step C, Example 1, to afford the desired compound. Yield: .59%; ¹H

NMR (CDCl₃): δ 2.38 (t, 2H, J=7.8 Hz), 3.51 (t, 2H, J=7.8 Hz), 6.89 (bs, 2H), 7.42

(m, 4H); orange solid, mp: 146-150 °C (petroleum ether).

EXAMPLE 4

(2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-furan-2-yl-methanone

The procedure of Example 1 was followed except that 2-acetylfuran (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(2-

furanoyl)acetonitrile (Steps A and B). Cyclohexanone (Aldrich), 2-(2-

furanoyl)acetonitrile, morpholine, and sulfur were reacted according to the

procedure of Step C, Example 1, to afford the desired compound. Yield: 40%; ¹H

NMR (CDCl₃): δ 1.63 (m, 2H), 1.82 (m, 2H), 2.28 (t, 2H, J=5.8 Hz), 2.57 (t, 2H,

J=5.8 Hz), 6.20 (bs, 2H), 6.53 (m, 1H), 6.99 (d, 1H, J= 3.4 Hz), 7.55 (d, 1H, J=3.4

Hz); yellow solid, mp: 121-122 °C (petroleum ether).

EXAMPLE 5

2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-thiophen-2-yl-methanone

The procedure of Example 1 was followed except that 2-acetylthiophene (Aldrich)

was used in place of acetophenone to prepare the corresponding 2-(thiophene-2-

carbonyl)acetonitrile (Steps A and B). Cyclohexanone (Aldrich), 2-(thiophene-2-

carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the

procedure of Step C, Example 1, to afford the desired compound. Yield: 56%; ¹H

NMR (CDCl₃): δ 1.59 (m, 2H), 1.81 (m, 2H), 2.20 (m, 2H), 2.54 (m, 2H), 6.10 (bs,

2H), 7.06 (dd, 1H, J=4.8 and 3.6 Hz), 7.38 (d, 1H, J=3.6 Hz), 7.60 (d, 1H, J=4.2 Hz);

orange solid, mp: 115-118 °C (petroleum ether).

EXAMPLE 6

(2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-naphthalen-1-yl-methanone

The procedure of Example 1 was followed except that 1'-acetonaphthone (Aldrich)

was used in place of acetophenone to prepare the corresponding 2-(naphthalen-1-

carbonyl)acetonitrile (Steps A and B). Cyclohexanone (Aldrich), 2-(naphthalen-1-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 73%; IR (KBr) cm^{-1} : 3335, 3235, 3124, 1559, 1430, 1290, 781; ^1H NMR (CDCl_3): δ 1.29 (m, 4H), 1.50 (t, 2H, $J=6.0$ Hz), 2.44 (t, 2H, $J=6.2$ Hz), 7.47 (m, 4H), 7.85 (m, 4H), 8.28 (d, 1H, $J=6.4$ Hz); orange solid, mp: 137-140 °C (ethanol).

EXAMPLE 7

(2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-naphthalen-1-yl-methanone

The procedure of Example 1 was followed except that 1'-acetonaphthone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(naphthalen-1-carbonyl)acetonitrile (Steps A and B). Cyclopentanone (Aldrich), 2-(naphthalen-1-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 89%; IR (KBr) cm^{-1} : 3328, 3102, 2853, 1582, 1444, 1290, 1255, 1032, 780; ^1H NMR (CDCl_3): δ 1.28 (m, 2H), 1.87 (t, 2H, $J=7.0$ Hz), 2.54 (t, 2H, $J=7.2$ Hz), 7.41 (d, 1H, $J=6.4$ Hz), 7.59 (m, 3H), 7.73 (d, 1H, $J=8.8$ Hz), 8.02 (d, 2H, $J=8.6$ Hz), 8.73 (bs, 2H); yellow solid, mp: 255-257 °C (petroleum ether).

EXAMPLE 8

(2-Amino-4,5-dimethylthiophen-3-yl)-naphthalen-1-yl-methanone

The procedure of Example 1 was followed except that 1'-acetonaphthone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(naphthalen-1-carbonyl)acetonitrile (Steps A and B). 2-Butanone (Aldrich), 2-(naphthalen-1-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 38%; IR (KBr) cm^{-1} : 3358, 3242, 1576, 1426, 1282, 1253, 781; ^1H NMR (CDCl_3): δ 1.16 (s, 3H), 2.07 (s, 3H), 7.17 (bs, 2H), 7.49 (m, 4H), 7.89 (m, 3H); yellow solid, mp: 195-197 °C (petroleum ether).

EXAMPLE 9

(2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-naphthalen-1-yl-methanone

The procedure of Example 1 was followed except that 1'-acetonaphthone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(naphthalen-1-carbonyl)acetonitrile (Steps A and B). 1-Benzyl-4-piperidone (prepared according to

the procedure of van der Klein *et al.*, (1999) *J. Med. Chem.* 42: 3629-3635), 2-(naphthalen-1-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 65%; IR (KBr) cm^{-1} : 3435, 1576, 1426, 1358, 1253, 784; ^1H NMR (CDCl_3): δ 1.53 (m, 2H), 2.30 (m, 2H), 3.38 (s, 2H), 3.54 (s, 2H), 7.43 (m, 11H), 7.88 (m, 3H); yellow solid, mp: 178-180 °C (petroleum ether).

EXAMPLE 10

N-[3-(Furan-2-carbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl]-acetamide

To a stirred solution of (2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-furan-2-yl-methanone (Example 4, 200 mg, 0.8 mmol) in dichloromethane (5 mL), cooled to 4 °C with an ice-water bath, was added triethylamine (0.12 mL, 0.88 mmol), followed by acetyl chloride (0.062 mL, 0.88 mmol). The mixture was warmed to room temperature, stirred for 12 hours, diluted with dichloromethane (5 mL), and washed with 5% aqueous HCl (5 mL), followed by saturated aqueous NaHCO_3 (5 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated, and the residue precipitated with ethyl acetate and petroleum ether. Yield: 69%; IR (KBr) cm^{-1} : 3448, 3118, 2931, 1677, 1606, 1529, 1466, 1432, 1267, 1063, 774; ^1H NMR (CDCl_3): δ 1.67 (m, 2H), 1.86 (m, 2H), 2.26 (s, 3H), 2.38 (t, 2H, $J=6.0$ Hz), 2.72 (t, 2H, $J=7.4$ Hz), 6.58 (m, 1H), 7.12 (d, 1H, $J=3.4$ Hz), 7.63 (s, 1H), 10.7 (s, 1H); yellow solid, mp: 126-127 °C (petroleum ether).

EXAMPLE 11

(2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-furan-2-yl-methanone

The procedure of Example 1 was followed except that 2-acetylfuran (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(2-furanoyl)acetonitrile (Steps A and B). Cyclopentanone (Aldrich), 2-(2-furanoyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 59%; IR (KBr) cm^{-1} : 3115, 1560, 1476, 1429, 1288, 1021, 746; ^1H NMR (CDCl_3): δ 2.3 (m, 2H), 2.73 (t, 4H, $J=6$ Hz), 6.53 (m, 1H), 6.81 (bs, 2H), 7.05 (d, 1H, $J=3.4$ Hz), 7.55 (s, 1H); yellow solid, mp: 149-153 °C (petroleum ether).

EXAMPLE 12

(2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-furan-2-yl-methanone

The procedure of Example 1 was followed except that 2-acetylfuran (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(2-furanoyl)acetonitrile (Steps A and B). 1-Benzyl-4-piperidone (van der Klein *et al.*, (1999) *J. Med. Chem.* 42: 3629-3635), 2-(2-furanoyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 62%; IR (KBr) cm^{-1} : 3337, 3231, 2931, 2821, 1579, 1485, 1433, 1364, 1287, 734; ^1H NMR (CDCl_3): δ 2.47 (t, 2H, $J=4.8$ Hz), 2.61 (t, 2H, $J=5.6$ Hz), 3.47 (s, 2H), 3.69 (s, 2H), 6.36 (bs, 2H), 6.51 (m, 1H), 7.01 (d, 1H, $J=3.4$ Hz), 7.31 (m, 5H), 7.55 (s, 1H); yellow solid, mp: 112-117 °C (petroleum ether).

EXAMPLE 13

(2-Amino-4,5-dimethylthiophen-3-yl)-furan-2-yl-methanone

The procedure of Example 1 was followed except that 2-acetylfuran (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(2-furanoyl)acetonitrile (Steps A and B). 2-Butanone (Aldrich), 2-(2-furanoyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 41 %; IR (KBr) cm^{-1} : 3265, 1573, 1474, 1426, 1293, 1158, 1021, 750; ^1H NMR (CDCl_3): δ 1.24 (s, 3H), 2.05 (s, 3H), 6.52 (bs, 2H), 7.00 (s, 1H), 7.31 (s, 1H), 7.54 (s, 1H); yellow solid, mp: 95-97 °C (petroleum ether).

EXAMPLE 14

(2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-benzofuran-2-yl-methanone

The procedure of Example 1 was followed except that benzofuran-2-yl methyl ketone (prepared according to the procedure of Farrar and Levine (1950), *J. Amer. Chem. Soc.*, 72: 4433-4436) was used in place of acetophenone to prepare the corresponding 2-(benzofuran-2-carbonyl)acetonitrile (Steps A and B).

Cyclohexanone (Aldrich), 2-(benzofuran-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 64%; IR (KBr) cm^{-1} : 3430, 2927, 1575, 1430, 752; ^1H NMR (CDCl_3): δ 1.56 (m, 2H), 1.81 (m, 2H), 2.29 (t, 2H, $J=5.8$ Hz), 2.59 (t, 2H, $J=6.2$ Hz), 6.55 (bs, 2H), 7.32 (m, 2H), 7.42 (t, 1H, $J=7.8$ Hz), 7.58 (d, 1H, $J=8.2$ Hz), 7.69 (d, 1H, $J=7.6$ Hz); yellow solid, mp: 86-89 °C (petroleum ether).

EXAMPLE 15

(2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-benzofuran-2-yl-methanone

The procedure of Example 1 was followed except that benzofuran-2-yl methyl ketone (Farrar and Levine (1950), *J. Amer. Chem. Soc.*, 72: 4433-4436) was used in place of acetophenone to prepare the corresponding 2-(benzofuran-2-carbonyl)acetonitrile (Steps A and B). Cyclopentanone (Aldrich), 2-(benzofuran-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 67%; IR (KBr) cm^{-1} : 3298, 1570, 1540, 1422, 1288, 1257, 1156, 1034, 884, 751; ^1H NMR (CDCl_3): δ 2.33 (m, 2H), 2.74 (t, 4H, $J=6.8$ Hz), 7.03 (bs, 2H), 7.31 (m, 2H), 7.42 (t, 1H, $J=7.2$ Hz), 7.57 (d, 1H, $J=8.2$ Hz), 7.69 (d, 1H, $J=7.6$ Hz); yellow solid, mp: 126-129 °C (petroleum ether).

EXAMPLE 16

(2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-benzofuran-2-yl-methanone

The procedure of Example 1 was followed except that benzofuran-2-yl methyl ketone (Farrar and Levine (1950), *J. Amer. Chem. Soc.*, 72: 4433-4436) was used in place of acetophenone to prepare the corresponding 2-(benzofuran-2-carbonyl)acetonitrile (Steps A and B). 1-Benzyl-4-piperidone (van der Klein *et al.*, (1999) *J. Med. Chem.* 42: 3629-3635), 2-(benzofuran-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 59%; IR (KBr) cm^{-1} : 3435, 1580, 1551, 1441, 749; ^1H NMR (CDCl_3): δ 2.45 (m, 2H), 2.59 (t, 2H, $J=5.2$ Hz), 3.48 (s, 2H), 3.69 (s, 2H), 6.64 (bs, 2H), 7.33 (m, 8H), 7.58 (d, 1H, $J=8$ Hz), 7.66 (d, 1H, $J=7.8$ Hz); yellow solid, mp: 83-87 °C (petroleum ether).

EXAMPLE 17

2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl-pyridin-2-yl-methanone

The procedure of Example 1 was followed except that 2-acetylpyridine (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(pyridin-2-carbonyl)acetonitrile (Steps A and B). Cyclopentanone (Aldrich), 2-(pyridin-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 52%; IR (KBr) cm^{-1} : 3338, 2853, 1582, 1560, 1453, 1424, 1355, 1307, 1278, 1146, 998, 759, 673. ^1H NMR (CDCl_3): δ 2.14 (m, 4H), 2.64 (m, 2H), 7.09 (bs, 2H), 7.36 (dd, 1H, $J=8.6$ and 5.2 Hz), 7.58 (d, 1H, $J=7.6$ Hz), 7.80 (m, 1H), 8.62 (d, 1H, $J=4.6$ Hz); yellow solid, mp: 143-146 °C (petroleum ether).

EXAMPLE 18

(2-Amino-4,5-dimethylthiophen-3-yl)-benzofuran-2-yl-methanone

The procedure of Example 1 was followed except that benzofuran-2-yl methyl ketone (Farrar and Levine (1950), *J. Amer. Chem. Soc.*, 72: 4433-4436) was used in place of acetophenone to prepare the corresponding 2-(benzofuran-2-carbonyl)acetonitrile (Steps A and B). 2-Butanone (Aldrich), 2-(benzofuran-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 44%; IR (KBr) cm^{-1} : 3305, 2922, 2852, 1574, 1434, 1257, 1159, 1111, 881, 802, 750; ^1H NMR (CDCl_3): δ 1.87 (s, 3H), 2.19 (s, 3H), 6.31 (bs, 2H), 7.32 (d, 2H, $J=7$ Hz), 7.38 (t, 1H, $J=7.4$ Hz), 7.57 (d, 1H, $J=8.2$ Hz), 7.69 (d, 1H, $J=7.4$ Hz); oil.

EXAMPLE 19

(2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-pyridin-2-yl-methanone

The procedure of Example 1 was followed except that 2-acetylpyridine (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(pyridin-2-carbonyl)acetonitrile (Steps A and B). Cyclohexanone (Aldrich), 2-(pyridin-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 58%; IR (KBr) cm^{-1} : 3240, 2949, 1573, 1450, 1429, 1286, 1128, 999, 754, 676; ^1H NMR (CDCl_3): δ 1.46 (m, 2H), 1.71 (m, 4H), 2.50 (t, 2H, $J=6.2$ Hz), 6.99 (bs, 2H), 7.37 (t, 1H, $J=3$ Hz), 7.57 (d, 1H, $J=7.8$ Hz), 7.81 (t, 1H, $J=7.6$ Hz), 8.62 (d, 1H, $J=4.6$ Hz); yellow solid, mp: 191-193 °C (petroleum ether).

EXAMPLE 20

(2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-pyridin-2-yl-methanone

The procedure of Example 1 was followed except that 2-acetylpyridine (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(pyridin-2-carbonyl)acetonitrile (Steps A and B). 1-Benzyl-4-piperidone (van der Klein *et al.*, (1999) *J. Med. Chem.* 42: 3629-3635), 2-(pyridin-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 60%; IR (KBr) cm^{-1} : 3368, 1578, 1442, 1361, 1299, 1130, 746, 677; ^1H NMR (CDCl_3): δ 1.89 (t, 2H, $J=5.8$ Hz), 2.51 (t, 2H, $J=5.8$ Hz), 3.41 (s, 2H), 3.62 (s, 2H), 7.07 (bs, 2H), 7.32 (m, 6H), 7.54 (d, 1H, $J=7.8$

Hz), 7.80 (t, 1H, J=7.6 Hz), 8.63 (d, 1H, J=4.8 Hz); yellow solid, mp: 67-71 °C (petroleum ether).

EXAMPLE 21

(2-Amino-4,5-dimethylthiophen-3-yl)-pyridin-2-yl-methanone

The procedure of Example 1 was followed except that 2-acetylpyridine (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(pyridin-2-carbonyl)acetonitrile (Steps A and B). 2-Butanone (Aldrich), 2-(pyridin-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 39%; IR (KBr) cm^{-1} : 3233, 1565, 1436, 1418, 1279, 1114, 750, 672; ^1H NMR (CDCl_3): δ 1.46 (s, 3H), 2.12 (s, 3H), 6.76 (bs, 2H), 7.37 (t, 1H, J=7.0 Hz), 7.62 (d, 1H, J=7.6 Hz), 7.81 (t, 1H, J=7.6 Hz), 8.63 (d, 1H, J=4.6 Hz); yellow solid, mp: 136-139 °C (petroleum ether).

EXAMPLE 22

(2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-(4-bromonaphthalen-1-yl)-methanone

The procedure of Example 1 was followed except that 1-acetyl-4-bromonaphthalene (prepared according to the procedure of Dixon *et al.*, (1981) *Can. J. Chem.* 59: 2629-2641) was used in place of acetophenone to prepare the corresponding 2-(4-bromonaphthalene-1-carbonyl)acetonitrile (Steps A and B). Cyclopentanone (Aldrich), 2-(4-bromonaphthalene-1-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 67%; IR (KBr) cm^{-1} : 3333, 3110, 2851, 1576, 1443, 1289, 1254, 1032, 804, 780; ^1H NMR (CDCl_3): δ 1.29 (m, 2H), 1.81 (t, 2H, J=6.8 Hz), 3.31 (m, 2H), 7.34 (m, 1H), 7.53 (m, 4H), 7.71 (m, 1H), 7.95 (m, 1H), 8.64 (m, 1H); yellow solid, mp: 210-212 °C (petroleum ether).

EXAMPLE 23

(2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-(4-methoxynaphthalen-1-yl)-methanone

The procedure of Example 1 was followed except that 1-acetyl-4-methoxynaphthalene (prepared according to the procedure of Dixon *et al.*, (1981) *Can. J. Chem.* 59: 2629-2641) was used in place of acetophenone to prepare the corresponding 2-(4-methoxynaphthalene-1-carbonyl)acetonitrile (Steps A and B).

Cyclopentanone (Aldrich), 2-(4-methoxynaphthalene-1-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 71%; IR (KBr) cm^{-1} : 3351, 3243, 2852, 1581, 1433, 1261, 1242, 1162, 1091, 1023, 822, 762, 712; ^1H NMR (CDCl_3): δ 1.59 (m, 2H), 1.96 (m, 2H), 2.59 (t, 2H, $J=7.6$ Hz), 4.04 (s, 3H), 6.79 (d, 1H, $J=8$ Hz), 7.12 (bs, 2H), 7.34 (d, 1H, $J=8$ Hz), 7.48 (m, 2H), 7.89 (m, 1H), 8.30 (m, 1H); brown solid, mp: 214-215 °C (petroleum ether).

EXAMPLE 24

(2-Amino-5,6-dihydro-4*H*-cyclopenta[b]thiophen-3-yl)-(4-iodonaphthalen-1-yl)-methanone

The procedure of Example 1 was followed except that 1-acetyl-4-iodonaphthalene (prepared according to the procedure of Dixon *et al.*, (1981) *Can. J. Chem.* 59: 2629-2641) was used in place of acetophenone to prepare the corresponding 2-(4-iodonaphthalene-1-carbonyl)acetonitrile (Steps A and B). Cyclopentanone (Aldrich), 2-(4-iodonaphthalene-1-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 68%; IR (KBr) cm^{-1} : 3329, 3221, 3106, 2852, 1581, 1444, 1290, 1254, 780; ^1H NMR (CDCl_3): δ 1.28 (m, 2H), 1.81 (t, 2H, $J=7$ Hz), 3.34 (m, 2H), 7.36 (d, 1H, $J=6.8$ Hz), 7.54 (m, 2H), 7.66 (d, 1H, $J=9.0$ Hz), 7.97 (d, 2H, $J=8.6$ Hz), 8.65 (bs, 2H); yellow solid, mp: 253-255 °C (petroleum ether).

EXAMPLE 25

(2-Amino-5,6-dihydro-4*H*-cyclopenta[b]thiophen-3-yl)-(4-chloronaphthalen-1-yl)-methanone

The procedure of Example 1 was followed except that 1-acetyl-4-chloronaphthalene (prepared according to the procedure of Dixon *et al.*, (1981) *Can. J. Chem.* 59: 2629-2641) was used in place of acetophenone to prepare the corresponding 2-(4-chloronaphthalene-1-carbonyl)acetonitrile (Steps A and B). Cyclopentanone (Aldrich), 2-(4-chloronaphthalene-1-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 71%; IR (KBr) cm^{-1} : 3348, 3229, 3119, 1571, 1443, 1359, 1272, 1253, 1195, 962, 835, 787, 759; ^1H NMR (CDCl_3): δ 1.06 (m, 2H), 1.84 (t, 2H, $J=7.2$ Hz), 2.52 (m, 2H), 7.37 (d, 1H, $J=6.8$ Hz), 7.71 (m, 4H), 8.24 (d, 1H, $J=8.8$ Hz), 8.70 (bs, 2H); yellow solid, mp: 258-260 °C (petroleum ether).

EXAMPLE 26

(2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-iodonaphthalen-1-yl)-methanone

The procedure of Example 1 was followed except that 1-acetyl-4-iodonaphthalene

(Dixon *et al.*, (1981) *Can. J. Chem.* 59: 2629-2641) was used in place of acetophenone to prepare the corresponding 2-(4-iodonaphthalene-1-carbonyl)acetonitrile (Steps A and B). Cyclohexanone (Aldrich), 2-(4-iodonaphthalene-1-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 69%; IR (KBr) cm^{-1} : 3336, 3234, 3123, 2933, 1579, 1558, 1429, 1290, 1254, 1130, 780; ^1H NMR (CDCl_3): δ 1.28 (m, 4H), 1.59 (t, 2H, $J=6.4$ Hz), 2.42 (t, 2H, $J=6.2$ Hz), 7.26 (m, 2H), 7.49 (m, 3H), 8.87 (m, 3H); yellow solid, mp: 180-182 °C (petroleum ether).

EXAMPLE 27

(2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-methoxynaphthalen-1-yl)-methanone

The procedure of Example 1 was followed except that 1-acetyl-4-

methoxynaphthalene (Dixon *et al.*, (1981) *Can. J. Chem.* 59: 2629-2641) was used

in place of acetophenone to prepare the corresponding 2-(4-methoxynaphthalene-1-carbonyl)acetonitrile (Steps A and B). Cyclohexanone (Aldrich), 2-(4-

iodonaphthalene-1-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound.

Yield: 66%; IR (KBr) cm^{-1} : 3383, 3275, 2928, 1578, 1436, 1323, 1245, 1093, 733; ^1H NMR (CDCl_3): δ 1.28 (m, 4H), 1.48 (t, 2H, $J=7.4$ Hz), 2.35 (t, 2H, $J=6$ Hz), 3.98 (s, 3H), 6.78 (d, 1H, $J=8$ Hz), 7.21 (d, 1H, $J=8$ Hz), 7.40 (m, 2H), 7.79 (m, 1H), 8.19 (m, 3H); yellow solid, mp: 227-229 °C (petroleum ether).

EXAMPLE 28

(2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-chloronaphthalen-1-yl)-methanone

The procedure of Example 1 was followed except that 1-acetyl-4-chloronaphthalene

(Dixon *et al.*, (1981) *Can. J. Chem.* 59: 2629-2641) was used in place of

acetophenone to prepare the corresponding 2-(4-chloronaphthalene-1-

carbonyl)acetonitrile (Steps A and B). Cyclohexanone (Aldrich), 2-(4-chloronaphthalene-1-carbonyl)acetonitrile, morpholine, and sulfur were reacted

according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 68%; IR (KBr) cm^{-1} : 3356, 3253, 2928, 1573, 1428, 1286, 1254, 1132, 941, 787, 760; ^1H NMR (CDCl_3): δ 1.31 (m, 4H), 1.60 (t, 2H, $J=6.4$ Hz), 2.41 (t, 2H, $J=6.4$ Hz), 7.29 (m, 3H), 7.56 (m, 3H), 7.91 (d, 1H, $J=8$ Hz), 8.31 (d, 1H, $J=6.8$ Hz); yellow solid, mp: 179-181°C (petroleum ether).

EXAMPLE 29

(2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-bromonaphthalen-1-yl)-methanone

The procedure of Example 1 was followed except that 1-acetyl-4-bromonaphthalene (Dixon *et al.*, (1981) *Can. J. Chem.* 59: 2629-2641) was used in place of acetophenone to prepare the corresponding 2-(4-bromonaphthalene-1-carbonyl)acetonitrile (Steps A and B). Cyclohexanone (Aldrich), 2-(4-bromonaphthalene-1-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 69%; IR (KBr) cm^{-1} : 3336, 3234, 2932, 1579, 1558, 1427, 1290, 1253, 1129, 780; ^1H NMR (CDCl_3): δ 1.29 (m, 4H), 1.59 (t, 2H, $J=6$ Hz), 2.44 (t, 2H, $J=6$ Hz), 7.26 (m, 2H), 7.48 (m, 3H), 7.89 (m, 3H); yellow solid, mp: 176-178 °C (petroleum ether).

EXAMPLE 30

(2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-naphthalen-2-yl-methanone

The procedure of Example 1 was followed except that 2'-acetonaphthone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(naphthalene-2-carbonyl)acetonitrile (Steps A and B). Cyclohexanone (Aldrich), 2-(naphthalene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 78%; IR (KBr) cm^{-1} : 3392, 2929, 1560, 1424, 1292, 1128, 783; ^1H NMR (CDCl_3): δ 1.43 (m, 4H), 1.75 (m, 2H), 2.53 (t, 2H, $J=6.2$ Hz), 7.53 (m, 3H), 7.62 (d, 1H, $J=8.4$ Hz), 7.89 (m, 5H); yellow solid, mp: 95-97 °C (petroleum ether).

EXAMPLE 31

(2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-naphthalen-2-yl-methanone

The procedure of Example 1 was followed except that 2'-acetonaphthone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(naphthalene-2-carbonyl)acetonitrile (Steps A and B). Cyclopentanone (Aldrich), 2-(naphthalene-2-

carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 67%; IR (KBr) cm^{-1} : 3341, 3240, 2926, 1561, 1436, 1285, 1039, 760, 742; ^1H NMR (CDCl_3): δ 1.60 (m, 2H), 2.09 (m, 2H), 2.68 (m, 2H), 6.96 (bs, 2H), 7.53 (t, 2H, $J=4.4$ Hz), 7.60 (d, 1H, $J=6.4$ Hz), 7.89 (m, 4H); yellow solid, mp: 178-180 °C (petroleum ether).

EXAMPLE 32

(2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-naphthalen-2-yl-methanone

The procedure of Example 1 was followed except that 2'-acetonaphthone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(naphthalene-2-carbonyl)acetonitrile (Steps A and B). 1-Benzyl-4-piperidone (van der Klein *et al.*, (1999) *J. Med. Chem.* 42: 3629-3635), 2-(naphthalene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 78%; IR (KBr) cm^{-1} : 3415, 3313, 2926, 1578, 1458, 1407, 1358, 1128, 749; ^1H NMR (CDCl_3): δ 1.94 (t, 2H, $J=5.2$ Hz), 2.41 (t, 2H, $J=5.8$ Hz), 3.42 (s, 2H), 3.60 (s, 2H), 6.79 (bs, 2H), 7.31 (m, 4H), 7.53 (m, 2H), 7.62 (dd, 1H, $J=9.6$ and 1.4 Hz), 7.87 (m, 5H); yellow solid, mp: 174-177 °C (petroleum ether).

EXAMPLE 33

(2-Amino-4,5-dimethylthiophen-3-yl)-naphthalen-2-yl-methanone

The procedure of Example 1 was followed except that 2'-acetonaphthone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(naphthalene-2-carbonyl)acetonitrile (Steps A and B). 2-Butanone (Aldrich), 2-(naphthalene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 42%; IR (KBr) cm^{-1} : 3391, 2922, 1560, 1424, 1263, 1154, 782, 761; ^1H NMR (CDCl_3): δ 1.55 (s, 3H), 2.16 (s, 3H), 6.42 (bs, 2H), 7.54 (m, 2 H), 7.68 (m, 1H), 7.82 (d, 1H, $J=8.4$ Hz), 7.87 (m, 3H); oil.

EXAMPLE 34

(2-Amino-6-spiro(1,4-dioxolan-2-yl)-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-chlorophenyl)-methanone

The procedure of Example 1 was followed except that 4-chloroacetophenone

(Aldrich) was used in place of acetophenone to prepare the corresponding 2-(4-chlorobenzoyl)acetonitrile (Steps A and B). 1,4-Cyclohexanedione-*mono*-ethylene ketal (Aldrich), 2-(4-chlorobenzoyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 78%; IR (KBr) cm^{-1} : 3423, 3297, 1575, 1442, 1426, 1285, 1112, 1058, 949, 839, 678; ^1H NMR (CDCl_3): δ 1.66 (t, 2H, $J=6.4$ Hz), 2.00 (t, 2H, $J=6.2$ Hz), 2.74 (s, 2H), 3.99 (m, 4H), 6.77 (bs, 2H), 7.41 (m, 4H); pale yellow solid, mp: 191-193 °C (petroleum ether).

EXAMPLE 35

(2-Amino-5,6-dihydro-4*H*-cyclopenta[b]thiophen-3-yl)-thiophen-2-yl-methanone

The procedure of Example 1 was followed except that 2-acetylthiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(thiophene-2-carbonyl)acetonitrile (Steps A and B). Cyclopentanone (Aldrich), 2-(thiophene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 67%; IR (KBr) cm^{-1} : 3344, 3242, 3130, 1566, 1435, 1264, 1031, 771, 747; ^1H NMR (CDCl_3): δ 2.27 (m, 2H), 2.47 (t, 2H, $J=7.4$ Hz), 2.70 (t, 2H, $J=7$ Hz), 6.65 (bs, 2H), 7.06 (dd, 1H, $J=3.8$ and 4.8 Hz), 7.37 (dd, 1H, $J=1.0$ and 4.6 Hz), 7.53 (dd, 1H, $J=5.0$ and 1.2 Hz); yellow solid, mp: 133-134 °C (petroleum ether).

EXAMPLE 36

(2-Amino-4,5-dimethylthiophen-3-yl)-thiophen-2-yl-methanone

The procedure of Example 1 was followed except that 2-acetylthiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(thiophene-2-carbonyl)acetonitrile (Steps A and B). 2-Butanone (Aldrich), 2-(thiophene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 44%; IR (KBr) cm^{-1} : 3390, 3269, 1552, 1429, 1272, 852, 772; ^1H NMR (CDCl_3): δ 1.86 (s, 3H), 2.17 (s, 3H), 5.78 (bs, 2H), 7.07 (dd, 1H, $J=3.8$ and 4.8 Hz), 7.56 (dd, 1H, $J=2.8$ and 0.8 Hz), 7.58 (dd, 1H, $J=5.0$ and 0.8 Hz); orange solid, mp: 117-118 °C (petroleum ether).

EXAMPLE 37

(2-Amino-6-hydroxy-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-chloro-phenyl)-methanone

The procedure of Example 1 was followed except that 4-chloroacetophenone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(4-chlorobenzoyl)acetonitrile (Steps A and B). 4-Hydroxycyclohexanone (prepared according to the procedure of Suzuki, Noyori, and Hamanaka, (1981) *J. Amer. Chem. Soc.* 103: 5606-5607), 2-(4-chlorobenzoyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 56%; IR (KBr) cm^{-1} : 3354, 3242, 3146, 2912, 1573, 1557, 1426, 1294, 1074; 773; ^1H NMR (CDCl_3): δ 1.80 (m, 4H), 2.50 (dd, 1H, $J=12$ and 4.8 Hz), 2.85 (dd, 1H, $J=12$ and 4.8 Hz), 4.20 (bs, 1H), 6.74 (bs, 2H), 7.40 (m, 4H); pale yellow solid, mp: 176-177 °C (petroleum ether).

EXAMPLE 38

(2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-thiophen-2-yl-methanone

The procedure of Example 1 was followed except that 2-acetylthiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(thiophene-2-carbonyl)acetonitrile (Steps A and B). 1-Benzyl-4-piperidone (van der Klein *et al.*, (1999), *J. Med. Chem.* 42: 3629-3635), 2-(thiophene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 78%; IR (KBr) cm^{-1} : 3412, 2928, 1570, 1419, 1355, 1265, 1119, 700; ^1H NMR (CDCl_3): δ 2.35 (t, 2H, $J=5.2$ Hz), 2.59 (t, 2H, $J=5.6$ Hz), 3.47 (s, 2H), 3.67 (s, 2H), 6.26 (bs, 2H), 7.05 (m, 1H), 7.30 (d, 1H, $J=5.2$ Hz), 7.35 (m, 5H), 7.53 (d, 1H, $J=4$ Hz); yellow solid, mp: 122-123 °C (petroleum ether).

EXAMPLE 39

(2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(5-bromothiophen-2-yl)-methanone

The procedure of Example 1 was followed except that 2-acetyl-5-bromothiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(5-bromothiophene-2-carbonyl)acetonitrile (Steps A and B). Cyclohexanone (Aldrich), 2-(5-bromothiophene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 66%; IR (KBr) cm^{-1} : 3379, 3247, 2918, 1577, 1548, 1432, 1416, 1273, 761; ^1H NMR (CDCl_3): δ 1.63 (m, 2H), 1.79 (m, 2H), 2.24 (t, 2H, $J=5.8$ Hz), 2.55 (t, 2H, $J=5.8$ Hz), 6.11 (bs, 2H), 7.02 (d, 1H, $J=4$ Hz), 7.13 (d, 1H, $J=4$ Hz); orange solid,

mp: 160-163 °C (petroleum ether).

EXAMPLE 40

(2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-(5-bromothiophen-2-yl)-methanone

The procedure of Example 1 was followed except that 2-acetyl-5-bromothiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(5-bromothiophene-2-carbonyl)acetonitrile (Steps A and B). Cyclopentanone (Aldrich), 2-(5-bromothiophene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 73%; IR (KBr) cm^{-1} : 3349, 3236, 3130, 1590, 1549, 1431, 1414, 1269, 975; ^1H NMR (CDCl_3): δ 2.285 (m, 2H), 2.51 (t, 2H, $J=7.4$ Hz), 2.70 (t, 2H, $J=7.4$ Hz), 6.64 (bs, 2H), 7.02 (d, 1H, $J=4$ Hz), 7.13 (d, 1H, $J=4$ Hz); red solid, mp: 154-156 °C (petroleum ether).

EXAMPLE 41

(2-Amino-4,5-dimethylthiophen-3-yl)-(5-bromothiophen-2-yl)-methanone

The procedure of Example 1 was followed except that 2-acetyl-5-bromothiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(5-bromothiophene-2-carbonyl)acetonitrile (Steps A and B). 2-Butanone (Aldrich), 2-(5-bromothiophene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 51%; IR (KBr) cm^{-1} : 3348, 1559, 1448, 1413, 1388, 1318, 1263, 974, 769; ^1H NMR (CDCl_3): δ 2.16 (s, 6H), 5.90 (bs, 2H), 7.02 (d, $J=4$ Hz, 1H), 7.11 (d, 1H, $J=4$ Hz); orange solid, mp: 128-130 °C (petroleum ether).

EXAMPLE 42

(2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-(5-bromothiophen-2-yl)-methanone

The procedure of Example 1 was followed except that 2-acetyl-5-bromothiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(5-bromothiophene-2-carbonyl)acetonitrile (Steps A and B). 1-Benzyl-4-piperidone (van der Klein *et al.*, (1999), *J. Med. Chem.* 42: 3629-3635), 2-(5-bromothiophene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 72%; IR (KBr) cm^{-1} : 3411, 2923, 1570, 1411, 1314, 978; ^1H NMR (CDCl_3): δ 2.38 (t, $J=5.4$

Hz, 2H), 2.59 (t, 2H, J=5.4 Hz), 3.48 (s, 2H), 3.67 (s, 2H), 6.28 (bs, 2H), 7.01 (d, 1H, J=4 Hz), 7.15 (d, 1H, J=4 Hz), 7.32 (m, 5H); brown solid, mp: 87-89 °C (petroleum ether).

5 **EXAMPLE 43**

(2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(5-chlorothiophen-2-yl)-methanone

The procedure of Example 1 was followed except that 2-acetyl-5-chlorothiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(5-chlorothiophene-2-carbonyl)acetonitrile (Steps A and B). Cyclohexanone (Aldrich), 2-(5-chlorothiophene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 76%; IR (KBr) cm^{-1} : 3349, 3237, 3131, 2911, 1577, 1547, 1430, 1281, 1006, 765; ^1H NMR (CDCl_3): δ 1.59 (m, 2H), 1.65 (m, 2H), 2.35 (t, 2H, J=5.8 Hz), 2.55 (t, 2H, J=5.8 Hz), 6.07 (bs, 2H), 6.88 (d, 1H, J=4 Hz), 7.16 (d, 1H, J= 4 Hz); yellow solid, mp: 173-175 °C (petroleum ether).

EXAMPLE 44

(2-Amino-5,6-dihydrocyclopenta[b]thiophen-3-yl)-(5-chlorothiophen-2-yl)-methanone

The procedure of Example 1 was followed except that 2-acetyl-5-chlorothiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(5-chlorothiophene-2-carbonyl)acetonitrile (Steps A and B). Cyclopentanone (Aldrich), 2-(5-chlorothiophene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 69%; IR (KBr) cm^{-1} : 3351, 3244, 3132, 2851, 1590, 1550, 1426, 1270, 1002, 813, 698; ^1H NMR (CDCl_3): δ 2.28 (m, 2H), 2.52 (t, 2H, J=7.2 Hz), 2.70 (t, 2H, J=7.2 Hz), 6.62 (bs, 2H), 6.88 (d, 1H, J= 4 Hz), 7.16 (d, 1H, J= 4 Hz); red solid, mp: 170-171 °C (petroleum ether).

EXAMPLE 45

(2-Amino-4,5-dimethylthiophen-3-yl)-(5-chlorothiophen-2-yl)-methanone

The procedure of Example 1 was followed except that 2-acetyl-5-chlorothiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(5-chlorothiophene-2-carbonyl)acetonitrile (Steps A and B). 2-Butanone (Aldrich), 2-(5-chlorothiophene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted

according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 46%; IR (KBr) cm^{-1} : 3377, 3259, 2918, 1551, 1424, 1326, 1266, 1003, 764; ^1H NMR (CDCl_3): δ 1.90 (s, 3H), 2.17 (s, 3H), 5.77 (bs, 2H), 6.89 (d, 1H, $J=4$ Hz), 7.16 (d, 1H, $J=4$ Hz); red solid, mp: 125-127 °C (petroleum ether).

5

EXAMPLE 46

(2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-(5-chloro-thiophen-2-yl)-methanone

The procedure of Example 1 was followed except that 2-acetyl-5-chlorothiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(5-chlorothiophene-2-carbonyl)acetonitrile (Steps A and B). 1-Benzyl-4-piperidone (van der Klein *et al.*, (1999) *J. Med. Chem.* 42: 3629-3635), 2-(5-chlorothiophene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 63%; IR (KBr) cm^{-1} : 3306, 2956, 2807, 1715, 1574, 1428, 1354, 1122, 1008, 742, 699; ^1H NMR (CDCl_3): δ 2.39 (m, 2H), 2.59 (t, 2H, $J=5.2$ Hz), 3.45 (s, 2H), 3.67 (s, 2H), 6.26 (bs, 2H), 6.87 (d, 1H, $J=3.8$ Hz), 7.19 (d, 1H, $J=4$ Hz), 7.35 (m, 5H); yellow solid, mp: 81-83 °C (petroleum ether).

EXAMPLE 47

(2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-thiophen-3-yl-methanone

The procedure of Example 1 was followed except that 3-acetylthiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(thiophene-3-carbonyl)acetonitrile (Steps A and B). Cyclohexanone (Aldrich), 2-(thiophene-3-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 67%; IR (KBr) cm^{-1} : 3323, 3107, 2929, 1576, 1433, 1266, 1151, 1080, 825, 726; ^1H NMR (CDCl_3): δ 1.55 (m, 2H), 1.77 (m, 2H), 2.01 (t, 2H, $J=6$ Hz), 2.54 (t, 2H, $J=6.2$ Hz), 6.46 (bs, 2H), 7.28 (m, 2H), 7.58 (t, 1H, $J=2.2$ Hz); yellow solid, mp: 133-135 °C (petroleum ether).

EXAMPLE 48

(2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-thiophen-3-yl-methanone

The procedure of Example 1 was followed except that 3-acetylthiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(thiophene-3-carbonyl)acetonitrile (Steps A and B). Cyclopentanone (Aldrich), 2-(thiophene-3-

carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 71 %; IR (KBr) cm^{-1} : 3330, 3117, 2846, 1569, 1448, 1435, 1265, 855, 836, 757, 715; ^1H NMR (CDCl_3) δ 2.24 (m, 4H), 2.71 (m, 2H), 6.83 (bs, 2H), 7.33 (m, 2H), 7.56 (m, 1H); yellow solid, mp: 125-127 °C (petroleum ether).

EXAMPLE 49

(2-Amino-4,5-dimethylthiophen-3-yl)-thiophen-3-yl-methanone

The procedure of Example 1 was followed except that 3-acetylthiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(thiophene-3-carbonyl)acetonitrile (Steps A and B). 2-Butanone (Aldrich), 2-(thiophene-3-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 38%; IR (KBr) cm^{-1} : 3337, 3229, 3107, 1576, 1427, 1265, 1162, 855, 736, 719; ^1H NMR (CDCl_3): δ 1.71 (s, 3H), 2.15 (s, 3H), 6.17 (bs, 2H), 7.30 (d, $J=2.2$ Hz, 2H), 7.63 (t, 1H, $J=2$ Hz); yellow solid, mp: 122-123 °C (petroleum ether).

EXAMPLE 50

(2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-thiophen-3-yl-methanone

The procedure of Example 1 was followed except that 3-acetyl-thiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(thiophene-3-carbonyl)acetonitrile (Steps A and B). 1-Benzyl-4-piperidone (van der Klein *et al.*, (1999) *J. Med. Chem.* 42: 3629-3635), 2-(thiophene-3-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 68%; IR (KBr) cm^{-1} : 3350, 3234, 2805, 1578, 1524, 1429, 1257, 1147, 984, 856, 799, 722; ^1H NMR (CDCl_3): δ 2.14 (m, 2H), 2.54 (t, 2H, $J=5.6$ Hz), 3.43 (s, 2H), 3.65 (s, 2H), 6.61 (bs, 2H), 7.33 (m, 7H), 7.58 (m, 1H); yellow solid, mp: 131-133 °C (petroleum ether).

EXAMPLE 51

[2-Amino-6-(4-methoxyphenyl)-4H-1,5,7-trithia-inden-3-yl]-naphthalen-1-yl-methanone

The procedure of Example 1 was followed except that 1'-acetonaphthone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(naphthalene-1-carbonyl)acetonitrile (Steps A and B). 2-(4-Methoxyphenyl)-1,3-dithian-5-one

(prepared according to the procedure of Luettringhaus, Mohr, and Englehard, *J. Liebig's Ann. Chem.* (1963) 661: 84-94), 2-(naphthalene-1-carbonyl)-acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 77%; IR (KBr) cm^{-1} : 3412, 1607, 1578, 1509, 1420, 1303, 1254, 1176, 1112, 1029, 778; ^1H NMR (CDCl_3): δ 2.17 (s, 2H), 3.77 (s, 3H), 3.81 (s, 1H), 6.78 (d, 2H, $J=8.6$ Hz), 7.28 (bs, 2H), 7.29 (m, 2H), 7.51 (m, 5H), 7.93 (m, 2H); yellow solid, mp: 132-134 °C (petroleum ether).

EXAMPLE 52

[2-Amino-6-(4-methoxyphenyl)-4H-1,5,7-trithia-inden-3-yl]-(4-chloro-phenyl)-methanone

The procedure of Example 1 was followed except that 4-chloroacetophenone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(4-chlorobenzoyl)acetonitrile (Steps A and B). 2-(4-Methoxyphenyl)-1,3-dithian-5-one (Luettringhaus, Mohr, and Englehard, *J. Liebig's Ann. Chem.* (1963) 661: 84-94), 2-(4-chloro-benzoyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 74%; IR (KBr) cm^{-1} : 3436, 3311, 1607, 1578, 1509, 1432, 1255, 1174, 1090, 1025, 838; ^1H NMR (CDCl_3) δ 3.29 (d, 2H, $J=6.8$ Hz), 3.80 (s, 3H), 3.82 (s, 1H), 6.65 (bs, 2H), 6.88 (t, 2H, $J=8.6$ Hz), 7.35 (d, 2H, $J=8.6$ Hz), 7.40 (d, 2H, $J=8.4$ Hz), 7.57 (d, 2H, $J=8.4$ Hz); yellow solid, mp: 158-160 °C (petroleum ether).

EXAMPLE 53

[2-Amino-6-(4-methoxyphenyl)-4H-1,5,7-trithia-inden-3-yl]-thiophen-2-yl-methanone

The procedure of Example 1 was followed except that 2-acetylthiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(thiophene-2-carbonyl)acetonitrile (Steps A and B). 2-(4-Methoxyphenyl)-1,3-dithian-5-one (Luettringhaus, Mohr, and Englehard, *J. Liebig's Ann. Chem.* (1963) 661: 84-94), 2-(thiophene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 75%; IR (KBr) cm^{-1} : 3429, 3324, 1608, 1566, 1509, 1436, 1254, 1174, 1029, 838, 716; ^1H NMR (CDCl_3): δ 3.69 (d, 2H, $J=6.8$ Hz), 3.81 (s, 3H), 3.83 (s, 1H), 6.14 (bs, 2H), 6.87 (t, 2H, $J=8.8$ Hz), 7.11 (m, 1H), 7.38 (d, 2H, $J=8.8$ Hz), 7.56 (d, 1H, $J=3.2$ Hz), 7.62 (d, 1H, $J=5$ Hz); orange solid, mp: 138-140 °C (petroleum ether).

EXAMPLE 54

(2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(9H-fluoren-2-yl)-methanone

The procedure of Example 1 was followed except that 2-acetylfluorene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(fluorene-2-

carbonyl)acetonitrile (Steps A and B). 1-Benzyl-4-piperidone (van der Klein *et al.*, (1999) *J. Med. Chem.* 42: 3629-3635), 2-(fluorene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 73%; IR (KBr) cm^{-1} : 3410, 3311, 1602, 1578, 1471, 1355, 1264, 1230, 1123, 764, 748, 699; ^1H NMR (CDCl_3): δ 2.00 (t, 2H, J=5.2 Hz), 2.46 (t, 2H, J=5 Hz), 3.44 (s, 2H), 3.61 (s, 2H), 3.94 (s, 2H), 6.68 (bs, 2H), 7.32 (m, 7H), 7.55 (t, 2H, J=7.6 Hz), 7.69 (s, 1H), 7.79 (d, 2H, J=7.6 Hz); yellow solid, mp: 197-200 °C (petroleum ether).

Example 55

(2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophen-3-yl)-(9H-fluoren-2-yl)-methanone

[118] The procedure of Example I was followed except that 2-acetylfluorene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(fluorene-2-carbonyl)acetonitrile (Steps A and B). Cyclopentanone (Aldrich), 2-(fluorene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 68%; IR (KBr) cm^{-1} : 3400, 2928, 2846, 1685, 1560, 1430, 1268, 737; ^1H NMR (CDCl_3): δ 2.15 (m, 4H), 2.69 (m, 2H), 3.94 (s, 2H), 6.86 (bs, 2H), 7.36 (m, 3H), 7.54 (d, 1H, J=8 Hz), 7.58 (d, 1H, J=7.8 Hz), 7.89 (t, 2H, J=7.8 Hz); yellow solid, mp: 176-182 °C (petroleum ether).

Example 56

(2-Amino-6-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl)-(9H-fluoren-2-yl)-methanone

[119] The procedure of Example I was followed except that 2-acetylfluorene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(fluorene-2-carbonyl)acetonitrile (Steps A and B). 1-Benzyl-4-piperidone (van der Klein *et al.*, (1999) *J. Med. Chem.* 42: 3629-3635), 2-(fluorene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 73%; IR (KBr) cm^{-1} : 3410, 3311, 1602, 1578, 1471, 1355, 1264, 1230, 1123, 764, 748, 699; ^1H NMR (CDCl_3): δ 2.00 (t, 2H,

EXAMPLE 57

[2-Amino-6-[(methanesulfonyl)oxy]-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl]-(4-chlorophenyl)-methanone

The procedure of Example 1 was followed except that 4-chloroacetophenone

(Aldrich) was used in place of acetophenone to prepare the corresponding 2-(4-chlorobenzoyl)acetonitrile (Steps A and B). 4-(Methanesulfonyloxy)cyclo-hexanone (prepared according to the procedure of Yadav and Jeyaraj, (1998) *J. Org. Chem.*

63: 3474-3477), 2-(4-chlorobenzoyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired

compound. Yield: 56%; IR (KBr) cm^{-1} : 3429, 2928, 1577, 1432, 1349, 1172, 944; ^1H NMR (CDCl_3): δ 1.88 (t, 2H, $J=6.2$ Hz), 1.97 (t, 2H, $J=4.8$ Hz), 2.94 (m, 2H), 3.03 (s, 3H), 5.07 (m, 1H), 6.75 (bs, 2H), 7.41 (m, 4H); yellow solid, mp: 73-75 °C (petroleum ether).

EXAMPLE 58

[2-Amino-6-(4-chlorobenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl]-naphthalen-2-yl-methanone

The procedure of Example 1 was followed except that 2'-acetonaphthone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(naphthalene-2-carbonyl)acetonitrile (Steps A and B). 1-(4-Chlorobenzyl)-4-piperidone (prepared according to the procedure of van der Klein *et al.*, (1999) *J. Med. Chem.* 42: 3629-3635), 2-(naphthalene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound.

Yield: 68%; IR (KBr) cm^{-1} : 3392, 2963, 1715, 1577, 1423, 1262, 1088, 1016, 800; ^1H NMR (CDCl_3): δ 1.93 (t, 2H, $J=5.6$ Hz), 2.43 (t, 2H, $J=5.8$ Hz), 3.42 (s, 2H), 3.56 (s, 2H), 6.80 (bs, 2H), 7.26 (s, 4H), 7.59 (m, 3H), 7.92 (m, 4H); mp: 105-108 °C (petroleum ether).

EXAMPLE 59

2-Amino-6-(4-fluorobenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl]-naphthalen-2-yl-methanone

The procedure of Example 1 was followed except that 2'-acetonaphthone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(naphthalene-2-carbonyl)acetonitrile (Steps A and B). 1-(4-Fluorobenzyl)-4-piperidone (prepared according to the procedure of van der Klein *et al.*, (1999) *J. Med. Chem.* 42: 3629-3635), 2-(naphthalene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted

according to the procedure of Step C, Example 1, to afford the desired compound.
Yield: 69%; IR (KBr) cm^{-1} : 3401, 2928, 1577, 1508, 1424, 1263, 1221, 1130, 824;
 ^1H NMR (CDCl_3) δ 1.96 (t, 2H, $J=5.4$ Hz), 2.38 (t, 2H, $J=5.6$ Hz), 3.42 (s, 2H), 3.56
(s, 2H), 6.81 (bs, 2H), 6.98 (t, 2H, $J=8.8$ Hz), 7.27 (t, 2H, $J=6.2$ Hz), 7.56 (m, 2H),
5 7.90 (m, 5H); mp: 94-96 °C (petroleum ether).

EXAMPLE 60

(2-Amino-6-benzyl-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-naphthalen-2-yl-methanone

10 The procedure of Example 1 was followed except that 2'-acetonaphthone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(naphthalene-2-carbonyl)acetonitrile (Steps A and B). 4-Benzyl-cyclohexanone (prepared according to the procedure of Rosowsky *et al.*, (1999) *J. Med. Chem.* 42: 1007-1017), 2-(naphthalene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted
15 according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 61%; IR (KBr) cm^{-1} : 3369, 2914, 1569, 1424, 1285, 1252, 782; ^1H NMR (CDCl_3) δ 1.17 (m, 2H), 1.27 (m, 1H), 1.56 (m, 1H), 1.81 (m, 1H), 2.19 (m, 2H), 2.49 (d, 2H, $J=7$ Hz), 7.03 (bs, 2H), 7.29 (m, 6H), 7.48 (m, 5H), 7.88 (d, 1H, $J=8.8$ Hz); mp: 69-70 °C (petroleum ether).

EXAMPLE 61

[2-Amino-6-(2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl]-naphthalen-2-yl-methanone

The procedure of Example 1 was followed except that 2'-acetonaphthone (Aldrich)
25 was used in place of acetophenone to prepare the corresponding 2-(naphthalene-2-carbonyl)acetonitrile (Steps A and B). 1-(2-Fluorobenzyl)-4-piperidone (prepared according to the procedure of van der Klein *et al.*, (1999) *J. Med. Chem.* 42: 3629-3635), 2-(naphthalene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound.
30 Yield: 70%; IR (KBr) cm^{-1} : 3420, 3316, 2793, 1579, 1458, 1358, 1285, 1228, 1131, 762; ^1H NMR (CDCl_3) δ 1.95 (t, 2H, $J=5.6$ Hz), 2.45 (t, 2H, $J=5.4$ Hz), 3.49 (s, 2H), 3.66 (s, 2H), 6.61 (bs, 2H), 7.08 (m, 3H), 7.31 (m, 1H), 7.35 (d, 1H, $J=7.2$ Hz), 7.54 (t, 2H, $J=4.2$ Hz), 7.63 (d, 1H, $J=8.6$ Hz), 7.86 (m, 2H), 7.97 (s, 1H); mp: 183-185 °C (petroleum ether).

EXAMPLE 62

[2-Amino-6-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl]-naphthalen-2-yl-methanone

The procedure of Example 1 was followed except that 2'-acetonaphthone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(naphthalene-2-carbonyl)acetonitrile (Steps A and B). 1-(2-Chlorobenzyl)-4-piperidone (prepared according to the procedure of van der Klein *et al.*, (1999) *J. Med. Chem.* 42: 3629-3635), 2-(naphthalene-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound.

Yield: 68%; IR (KBr) cm^{-1} : 3419, 3317, 2918, 2792, 1600, 1578, 1461, 1410, 1359, 1282, 1135, 984, 781, 759; ^1H NMR (CDCl_3): δ 1.96 (t, 2H, $J=5.4$ Hz), 2.49 (t, 2H, $J=5.6$ Hz), 3.53 (s, 2H), 3.73 (s, 2H), 6.60 (bs, 2H), 7.19 (m, 4H), 7.46 (d, 1H, $J=6.6$ Hz), 7.52 (t, 2H, $J=6.4$ Hz), 7.61 (d, 1H, $J=8.4$ Hz), 7.88 (m, 2H), 7.99 (s, 1H); mp: 169-171 °C (petroleum ether).

EXAMPLE 63

[2-Amino-6-(3,4,5-trimethoxybenzyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-3-yl]-naphthalen-2-yl-methanone

The procedure of Example 1 was followed except that 2'-acetonaphthone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(naphthalene-2-carbonyl)acetonitrile (Steps A and B). 1-(3,4,5-Trimethoxybenzyl)-4-piperidone (prepared according to the procedure of van der Klein *et al.*, (1999) *J. Med. Chem.* 42: 3629-3635), 2-(naphthalene-2-carbonyl)-acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 89%; IR (KBr) cm^{-1} : 3394, 2933, 2831, 1578, 1421, 1358, 1233, 1125, 1005, 782; ^1H NMR (CDCl_3): δ 1.93 (t, 2H, $J=5.6$ Hz), 2.40 (t, 2H, $J=5.6$ Hz), 3.46 (s, 2H), 3.52 (s, 2H), 3.81 (s, 3H), 3.83 (s, 6H), 6.53 (s, 2H), 6.62 (bs, 2H), 7.53 (t, 2H, $J=4$ Hz), 7.62 (d, 1H, $J=8.8$ Hz), 7.87 (m, 3H), 7.98 (s, 1H); mp: 127-129 °C (petroleum ether).

EXAMPLE 64

(2-Amino-6-benzyl-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-thiophen-2-yl-methanone

The procedure of Example 1 was followed except that 2-acetylthiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(thiophen-2-carbonyl)acetonitrile (Steps A and B). 4-Benzyl-cyclohexanone (Rosowsky *et al.*,

(1999) *J. Med. Chem.* 42: 1007-1017), 2-(thiophen-2-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 72%; IR (KBr) cm^{-1} : 3465, 2925, 1554, 1425, 1270, 1041, 768, 730, 702; ^1H NMR (CDCl_3): δ 0.88 (m, 1H), 1.27 (m, 2H, 1.56 (m, 1H), 2.23 (m, 3H), 2.66 (dd, 2H, $J=7.2$ and 3Hz), 6.11 (bs, 2H), 7.04 (t, 1H, $J=4.4$ Hz), 7.23 (m, 6H), 7.52 (d, 1H, $J=4.8$ Hz); mp: 116-118 °C (petroleum ether).

EXAMPLE 65

(2-Amino-6-benzyl-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-thiophen-3-yl-methanone

The procedure of Example 1 was followed except that 3-acetylthiophene (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(thiophen-3-carbonyl)acetonitrile (Steps A and B). 4-Benzyl-cyclohexanone (Rosowsky *et al.*, (1999) *J. Med. Chem.* 42: 1007-1017), 2-(thiophen-3-carbonyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 65%; IR (KBr) cm^{-1} : 3401, 2920, 1560, 1547, 1419, 1260, 700; ^1H NMR (CDCl_3): δ 0.79 (m, 1H), 1.29 (m, 2H), 1.49 (m, 1H), 2.17 (m, 3H), 2.66 (m, 2H), 7.02 (bs, 2H), 7.28 (m, 8H); mp: 57-58 °C (petroleum ether).

EXAMPLE 66

(2-Amino-6-benzyl-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-(4-chlorophenyl)-methanone

The procedure of Example 1 was followed except that 4-chloroacetophenone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(4-chlorobenzoyl)acetonitrile (Steps A and B). 4-Benzylcyclohexanone (Rosowsky *et al.*, (1999) *J. Med. Chem.* 42: 1007-1017), 2-(4-chlorobenzoyl)acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 63%; IR (KBr) cm^{-1} : 3435, 2923, 1577, 1430, 1088, 700; ^1H NMR (CDCl_3): δ 0.88 (m, 1H), 1.28 (m, 2H), 1.72 (m, 1H), 2.25 (m, 3H), 2.59 (d, 2H, $J=7$ Hz), 6.70 (bs, 2H), 7.26 (m, 9H); mp: 60-62 °C (petroleum ether).

EXAMPLE 67

(2-Amino-6-benzyl-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)-naphthalen-2-yl-methanone

The procedure of Example 1 was followed except that 2'-acetonaphthone (Aldrich)

was used in place of acetophenone to prepare the corresponding 2-(naphthalene-2-carbonyl)acetonitrile (Steps A and B). 4-Benzyl-cyclohexanone (Rosowsky *et al.*, (1999) *J. Med. Chem.* 42: 1007-1017), 2-(naphthalene-2-carbonyl)-acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 60%; IR (KBr) cm^{-1} : 3419, 3315, 2912, 1596, 1568, 1456, 1282, 1130, 781, 749, 699; ^1H NMR (CDCl_3): δ 1.04 (m, 2H), 1.62, (m, 2H), 1.81 (m, 1H), 2.19 (m, 2H), 2.59 (d, 2H, $J=7.4$ Hz), 6.67 (bs, 2H), 7.19 (m, 4H), 7.56 (m, 4H), 7.88 (m, 4H); mp: 153 °C (petroleum ether).

EXAMPLE.68

[2-Amino-6-(4-nitrobenzyl)-4,5,6,7- tetrahydrobenzo[b]thiophen-3-yl]-naphthalen-2-yl-methanone

The procedure of Example 1 was followed except that 2'-acetonaphthone (Aldrich) was used in place of acetophenone to prepare the corresponding 2-(naphthalene-2-carbonyl)acetonitrile (Steps A and B). 1-(4-Nitrobenzyl)-4-piperidone (van der Klein *et al.*, (1999) *J. Med. Chem.* 42: 3629-3635), 2-(naphthalene-2-carbonyl)-acetonitrile, morpholine, and sulfur were reacted according to the procedure of Step C, Example 1, to afford the desired compound. Yield: 68%; IR (KBr) cm^{-1} : 3422, 1577, 1518, 1424, 1344, 858, 740; ^1H NMR (CDCl_3): δ 1.94 (t, 2H, $J=5.4$ Hz), 2.42 (t, 2H, $J=5.4$ Hz), 3.45 (s, 2H), 3.68 (s, 2H), 6.80 (bs, 2H), 7.58 (m, 5H), 7.91 (m, 4H), 8.15 (d, 2H, $J=8.6$ Hz); mp: 76-78 °C (petroleum ether).

EXAMPLE 69. PHARMACEUTICAL FORMULATIONS

(A) Transdermal System - for 1000 patches

| Ingredients | Amount |
|---------------------------|--------|
| Active compound | 100g |
| Silicone fluid | 450g |
| Colloidal silicon dioxide | 2g |

The silicone fluid and active compound are mixed together and the colloidal silicone dioxide is added to increase viscosity. The material is then dosed into a subsequent heat sealed polymeric laminate comprised of the following: polyester release liner, skin contact adhesive composed of silicone or acrylic polymers, a control membrane which is a polyolefin, and an impermeable backing membrane made of a

polyester multilaminate. The resulting laminated sheet is then cut into 10 sq. cm patches

(B) Oral Tablet - For 1000 Tablets

5

| Ingredients | Amount |
|--------------------|--------|
| Active compound | 50g |
| Starch | 50g |
| Magnesium Stearate | 5g |

The active compound and the starch are granulated with water and dried. Magnesium stearate is added to the dried granules and the mixture is thoroughly blended. The blended mixture is compressed into tablets.

10

(C) Injection - for 1000, 1 mL Ampules

| Ingredients | Amount |
|---------------------|-------------|
| Active compound | 10g |
| Buffering Agents | q.s. |
| Propylene glycol | 400mg |
| Water for injection | q.s. 1000mL |

The active compound and buffering agents are dissolved in the propylene glycol at about 50°C. The water for injection is then added with stirring and the resulting solution is filtered, filled into ampules, sealed and sterilized by autoclaving.

15

(D) Continuous Injection - for 1000 mL

| Ingredients | Amount |
|---------------------|-----------------|
| Active compound | 10g |
| Buffering agents | q.s. |
| Water for injection | q.s. 1000m L |

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents, modifications and variations to the specific embodiments of the invention described herein. For example, other excipients may be utilized in preparing the pharmaceutical formulations. In addition, some of the compounds described herein contain one or more asymmetric centers and may therefore give rise to enantiomers and diastereomers as well as their racemic and resolved, enantiomerically pure or diastereomerically pure forms, and pharmaceutically acceptable salts thereof. Moreover, it will be appreciated that the general representation of such paired variables as R^3 and R^4 , in formula IA, is not to be construed as to represent a particular orientation of the paired members. Accordingly, it is not intended that the present invention be limited to the specifics of the foregoing description of the preferred embodiments and example compounds, but rather as being limited only by the scope of the 'invention as defined in the claims appended hereto, including enantiomeric, diastereomeric and pharmaceutical salt forms.